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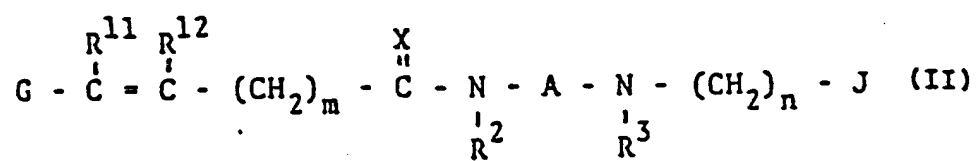
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(94) Butenoic or propenoic acid derivative.

(97) A butenoic or propenoic acid derivative having the following formula in which G is an aryl or a heterocyclic ring, R11 and R12 are hydrogen or an alkyl, X is sulfur or oxygen, R2 and R3 are hydrogen, an substituent such as an alkyl and J is pyridyl or phenyl having substituents and a heterocyclic ring may be formed between R2, R3 and J is provided here and is useful in the pharmacological field.



Butenolic or propenolic acid derivative

The invention relates to a butenolic or propenolic acid derivative having phenyl or a heterocyclic ring at its omega position. It is useful as a drug, in particular having an excellent coronary vasodilating and heart rate lowering effect.

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(Prior arts)

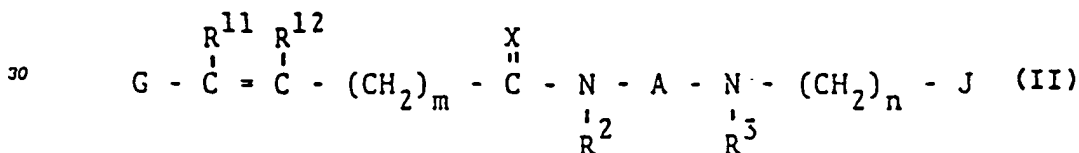
In countries of Europe and America, cardiovascular diseases head the list of death causes. In Japan, although cerebrovascular diseases such as cerebral apoplexy ranked high in the list of the death causes, ischemic heart disease has prominently increased recently, as the life-style and eating habit of Japanese have neared those of European and American.

Ischemic heart disease generally refers to a series of heart diseases caused when the supply of oxygen to cardiac muscle cannot make up for myocardial oxygen consumption. Representative examples thereof include coronary sclerosis, acute cardiac infarction and angina pectoris. Although nitro drugs, calcium antagonists and β -blockers are now generally used for the treatment of these diseases, no decisively effective drug has been found as yet, so that it is highly expected to develop a novel drug more excellent than those of the prior art.

20 (Summary of the invention)

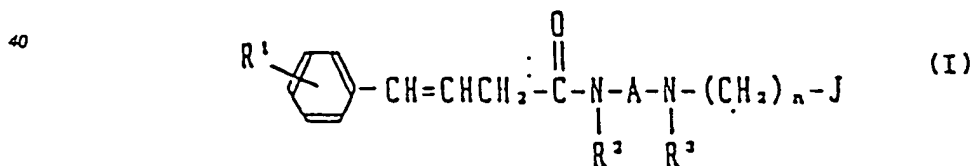
Under these circumstances, the inventors of the present invention have attempted to develop a new type of a remedy for ischemic heart disease. Particularly, the inventors have long studied to find out a compound which exhibits excellent coronary vasodilating and heart rate lowering effects.

25 The invention provides a butenolic or propenolic acid derivative having the formula (II) and a pharmacologically acceptable salt thereof:



35 which is defined by each of the following definitions (I), (II) and (III):

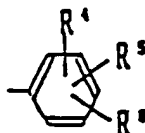
(I) having the formula (I) in which in the formula (II) G is R¹-phenyl, R¹¹ and R¹² each are hydrogen, m is one and X is oxygen,



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wherein R¹ is a hetero-aryl group, R² and R³ each are hydrogen, a lower alkyl, a cycloalkyl or an allyl group, or R² and R³ may form a 5- to 7-membered saturated heterocyclic ring together with the nitrogen atom to which they are bonded, A is an alkylene group having 1 to 6 carbon atoms, which alkylene may have a lower alkyl, a lower alkoxy or hydroxy, J is pyridyl or a phenyl having substituents R⁴, R⁵ and R⁶:

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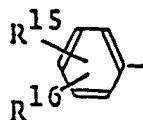
which R4, R5 and R6 each are hydrogen, a halogen atom, a lower alkyl, a lower alkoxy, hydroxy, nitro, cyano, trifluoromethyl, an alkylsulfonyloxy, -NR7R8, R7 and R8 being hydrogen or a lower alkyl, or an alkanolamino, or two of R4, R5 and R6 may form an alkylenedioxy together with two adjacent carbon atoms on the phenyl, or R4, R5 and R6 may form a 5- to 7-membered ring together with the -(CH2)-, and n is an integer of from 1 to 6;

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(II) having the formula (II) in which:

G is naphthyl or a phenyl having substituents R15 and R16:

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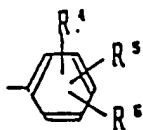
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R15 and R16 being hydrogen, a lower alkyl, a lower alkoxy, a halogen, -NR7R8, R7 and R8 being hydrogen or a lower alkyl, cyano, trifluoromethyl, an alkanoylamino, trifluoroalkoxy, an alkylsulfonyl, nitro, hydroxyl, an alkylthio, an alkylsulfonylamino, an alkylcarbonylamino or a carbamoyl, or R15 and R16 may form a cyclic ring together with oxygen between two adjacent carbon atoms, R11 and R12 each are hydrogen, cyano, a lower alkyl, or a halogen or they may form a cyclic ring together with oxygen and the carbon on the phenyl, m is zero or 1, X is oxygen or sulfur, R2 and R3 each are hydrogen, a lower alkyl, a lower alkoxy, a cycloalkyl, a trifluoroalkyl or a lower alkenyl, or R2 and R3 may form a 5- to 7-membered saturated heterocyclic ring together with the nitrogen atom to which they are bonded, or R2 may form a ring together with R12, or R3 may form a ring having a nitrogen atom together with the -(CH2)n-, R2 may form a 5- to 7-membered saturated heterocyclic ring together with A, R3 may form a 5- to 7-membered saturated heterocyclic ring together with A, A is an alkylene group having 1 to 6 carbon atoms, which alkylene may have a lower alkyl group, n is an integer of 1 to 6, J is pyridyl or a phenyl having substituents R4, R5 and R6:

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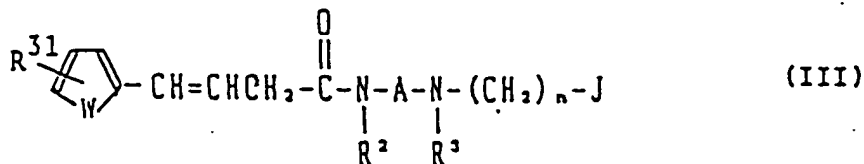


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which R4, R5 and R6 each are hydrogen, a halogen atom, a lower alkyl, a lower alkoxy, hydroxy, nitro, trifluoromethyl, an alkylsulfonyloxy, -NR7R8, R7 and R8 being hydrogen or a lower alkyl, or an alkanoylamino, or two of R4, R5 and R6 may form an alkylenedioxy together with two adjacent carbon atoms on the phenyl, or J may form a cyclic ring having a nitrogen together with the group -(CH2)n-; and (III) having the formula (III) in which in the formula (II) R11 and R12 are hydrogen, X is oxygen,

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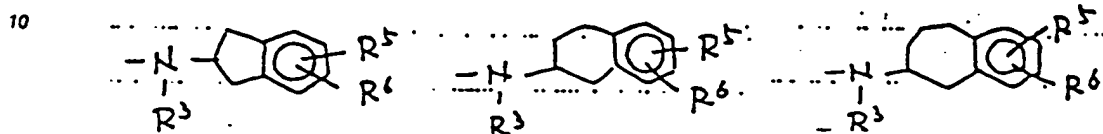


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wherein R31 is a hetero-aryl group, R2 and R3 each are hydrogen, a lower alkyl, a cycloalkyl or allyl, or R3 may form a 5- to 7-membered saturated heterocyclic ring together with the nitrogen and the -(CH2)n-, or R3 may form a 5- to 7-membered cyclic heteroring having nitrogen or nitrogen and oxygen together with A and

the nitrogen, A is an alkylene having 1 to 3 carbon atoms which may have a lower alkyl, hydroxy or a lower alkoxy group, W is oxygen, sulfur, vinylene ($-C=C-$) or azomethyne ($-N=CH-$), J is pyridyl or a phenyl having substituents R4, R5 and R6, which is hydrogen, a halogen, a lower alkyl, a lower alkoxy, hydroxy, nitro, cyano, trifluoromethyl, an alkylsulfonyloxy, -NR7R8, R7 and R8 being hydrogen or a lower alkyl group, or an alkanoylamino, or two of R4, R5 and R6 may form an alkylenedioxy together with two adjacent carbon atoms on the phenyl, one of R4, R5 and R6 may form a 5- to 7-membered cyclic ring together with the group $-(CH_2)_n-$, n is an integer of 1 to 6, $-(CH_2)_n-$ may have a lower alkyl.

When one of R4, R5 and R6 forms a ring with $-(CH_2)_n-$, the following are preferable:



In the above shown definitions I, II and III, two or more symbols are defined independently of each other when they are defined at the same time. Namely they may have either the same definitions as each other or different definitions from each other.

The pharmacologically acceptable salt according to the present invention includes inorganic acid salts such as hydrochloride, sulfate, hydrobromide and phosphate and organic acid salts such as formate, acetate, trifluoroacetate, maleate, fumarate, tartrate, methanesulfonate, benzenesulfonate and toluenesulfonate.

Although the compound of the present invention has an asymmetric carbon atom depending upon the kind of a substituent to be present as optical isomers, it is a matter of course that these optical isomers fall within the scope of the present invention.

The compound of the invention includes the three groups of its embodiments, (I), (II) and (III):

(I) a 4-phenyl-3-butenic acid derivative having the formula (I) and the definition (I) and a pharmacologically acceptable salt thereof;

(II) a butenoic or propionic acid derivative having the formula (II) and the definition (II) and a pharmacologically acceptable salt thereof; and

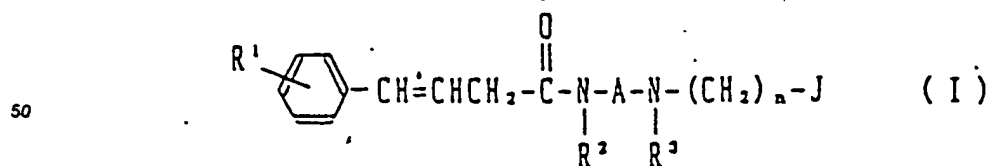
(III) a 4-aryl-3-butenic acid derivative having the formula (III) and the definition (III) and a pharmacologically acceptable salt thereof.

The compound of the invention will be described below more in detail in reference to the embodiments (I), (II) and (III).

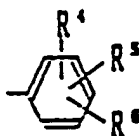
Embodiment (I)

The inventors of the present invention have long studied to find out a compound satisfying the above object and have found that a 4-phenyl-3-butenic acid derivative represented by the general formula (I) can attain the above object.

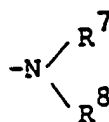
Namely, the present invention relates to a 4-phenyl-3-butenic acid derivative represented by the following general formula or a pharmacologically acceptable salt thereof:



wherein R1 stands for a hetero-aryl group, R2 and R3, which may be the same or different, each stand for a hydrogen atom, a lower alkyl group, a cycloalkyl group or an allyl group, or R2 and R3 form a 5- to 7-membered saturated heterocyclic ring together with the nitrogen atom to which they are bonded, A stands for an alkylene group having 1 to 6 carbon atoms, with the proviso that a lower alkyl group may be bonded to any carbon of the alkylene group, J stands for a group



{ in which R^4 , R^5 and R^6 which may be the same or different, each stand for a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group, a nitro group, a cyano group, a trifluoromethyl group, an alkylsulfonyloxy group, a group



(in which R^7 and R^8 , which may be the same or different, each stand for a hydrogen atom or a lower alkyl group) or an alkanoylamino group, and two of R^4 , R^5 and R^6 may form an alkylene-dioxy group between adjacent carbon atoms or R^4 , R^5 or R^6 may form a 5- to 7-membered ring together with the group $-(CH_2)_n$ or a pyridyl group, and n is an integer of 1 to 6.

It is preferable that R^1 is imidazolyl such as 1-imidazolyl or pyrrolyl such as 1-pyrrolyl and 3-pyrrolyl and n is an integer of 1 to 3.

It is also preferable that J is the phenyl having a substituent(s) such as *m,p*-dimethoxyphenyl, *m*-dimethoxyphenyl and *m,m,p*-trimethoxyphenyl, R^4 is a lower alkoxy, R^5 is a lower alkoxy and R^6 is hydrogen.

It is preferable that R^1 is an imidazolyl, R^2 is hydrogen, R^3 is methyl, J is the phenyl having a substituent(s) and R^4 , R^5 and R^6 each are hydrogen or a lower alkoxy.

It is preferable that R^1 is an imidazolyl, R^2 is hydrogen, R^3 is methyl and J is *m,p*-dimethoxyphenyl.

The lower alkyl group defined with respect to R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 in formula (I) stands for a straight-chain or branched alkyl group having 1 to 6 carbon atoms and examples thereof include methyl, ethyl, *n*-propyl, *n*-butyl, isopropyl, isobutyl, 1-methylpropyl, *tert*-butyl, *n*-pentyl, 1-ethylpropyl isoamyl and *n*-hexyl groups, among which methyl and ethyl groups are most preferred.

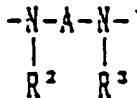
The lower alkoxy group defined with respect to R^4 , R^5 and R^6 stands for an alkoxy group derived from a lower alkyl group defined above.

The cycloalkyl group defined with respect to R^2 and R^3 stands for a 3- to 6-membered cycloalkyl group and preferred examples thereof include cyclopentyl and cyclohexyl groups.

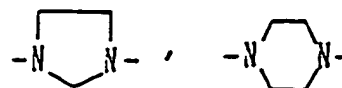
The hetero-aryl group defined with respect to R^1 stands for a substituted or unsubstituted heterocyclic group, the heterocyclic ring of which may contain one or more nitrogen, oxygen or sulfur atoms. Examples thereof include imidazolyl groups such as 1-imidazolyl and 2-imidazolyl groups; pyridyl groups such as 3-pyridyl and 4-pyridyl groups; pyrrolyl groups such as 1-pyrrolyl and 3-pyrrolyl groups; nitrogenous hetero-aryl groups such as pyrazolyl, indolyl, indazolyl, isoquinolyl, quinolyl, quinoxaliny, quinazolinyl and imidazopyridyl groups and hetero-aryl groups containing not only a nitrogen atom but also an oxygen atom such as oxazolyl and isoxazolyl groups, among which 1-imidazolyl group is most preferred.

Alternatively, the hetero-aryl group may be substituted with a lower alkyl group such as a methyl group.

When R^2 and R^3 form a 5- to 7-membered saturated heterocyclic ring together with the nitrogen atom to which they are bonded, the group represented by the formula



is, for example, a group represented by the formula:



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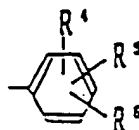
The alkylsulfonyloxy group defined with respect to R^4 , R^5 and R^6 may be one derived from a lower alkyl group described above, while the alkanoylamino group may be one derived from a lower alkyl group described above.

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A stands for an alkylene group having 1 to 6 carbon atoms, preferably one having about 3 carbon atoms. The alkylene group may have an alkyl group such as a methyl group bonded to any carbon atom thereof.

J stands for a group represented by the formula:

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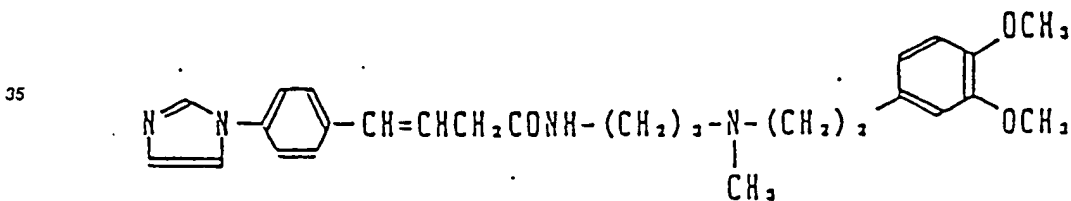
(wherein R^4 , R^5 and R^6 are each as defined above) or a pyridyl group. It is preferable that R^4 , R^5 and R^6 are each a lower alkoxy group having 1 to 3 carbon atoms, still preferably a methoxy group. The pyridyl group includes 2-pyridyl, 3-pyridyl and 4-pyridyl groups.

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Preferable compounds are:

(E)-N-[3-(N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

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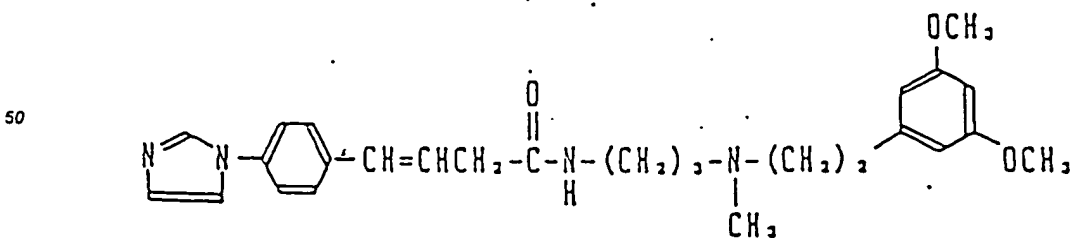


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(E)-N-[3-(N'-(2-(3,5-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

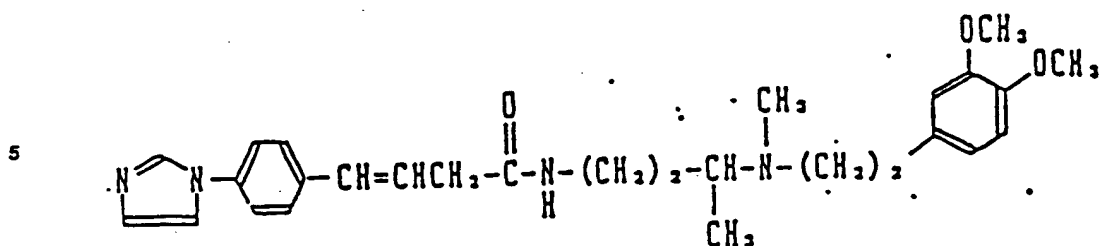
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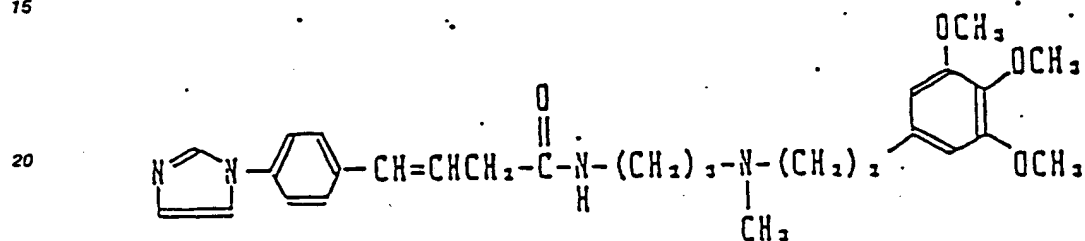
(E)-N-[3-(N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)butyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide



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(E)-N-[3-((N'-(2-(3,4,5-Trimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

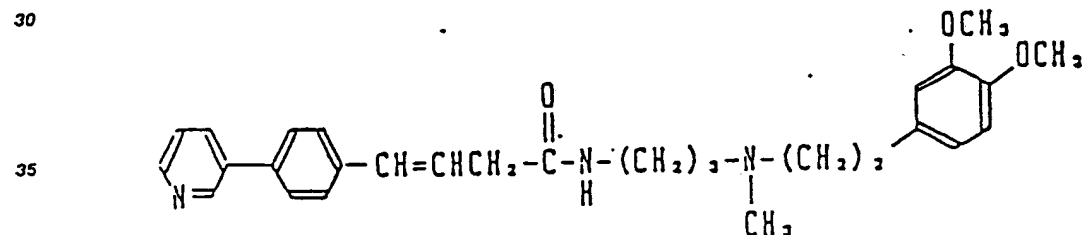
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(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(3-pyridyl)phenyl)-3-butenamide

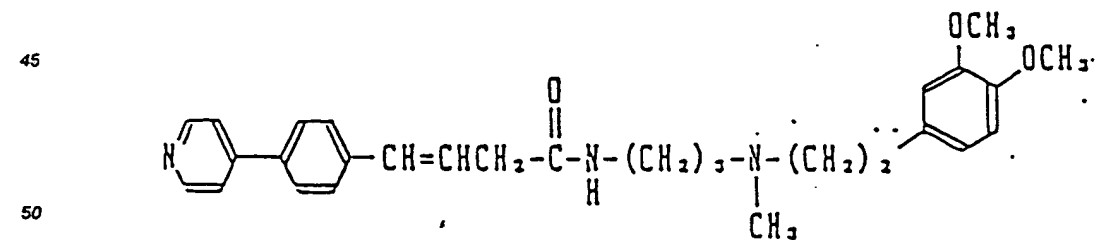
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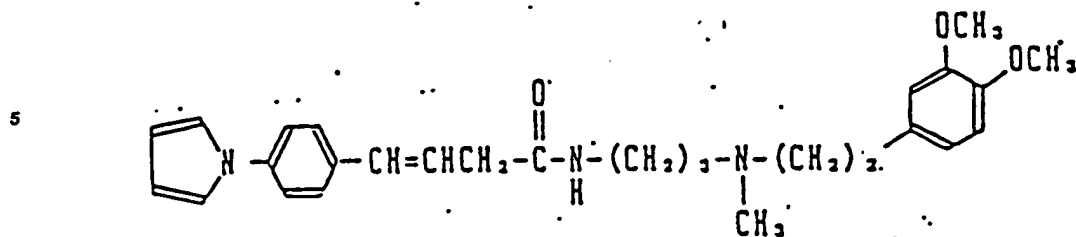
(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(4-pyridyl)phenyl)-3-butenamide

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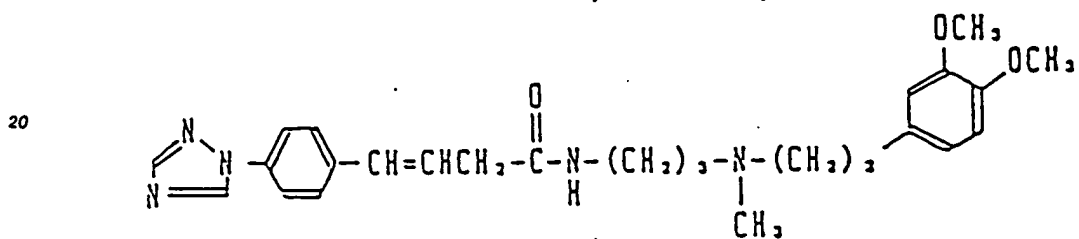
(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-pyrrol-1-yl)phenyl)-3-butenamide



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(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-1,2,4-triazol-1-yl)-phenyl)-3-butenamide

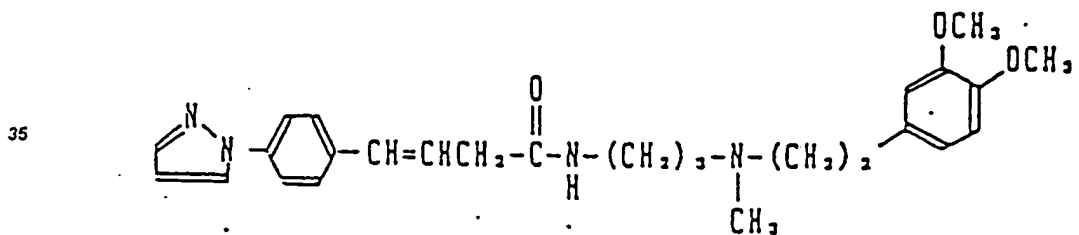
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(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-pyrazol-1-yl)phenyl)-3-butenamide

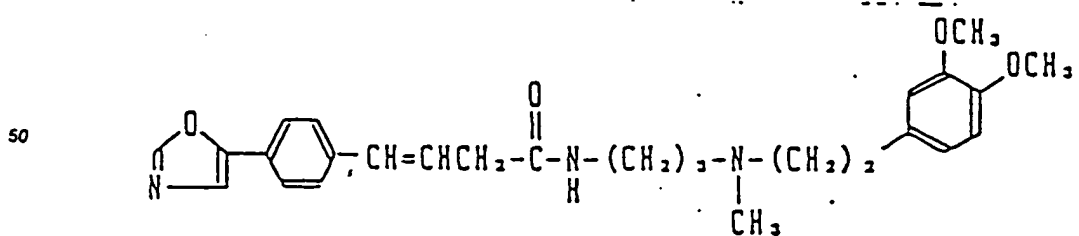
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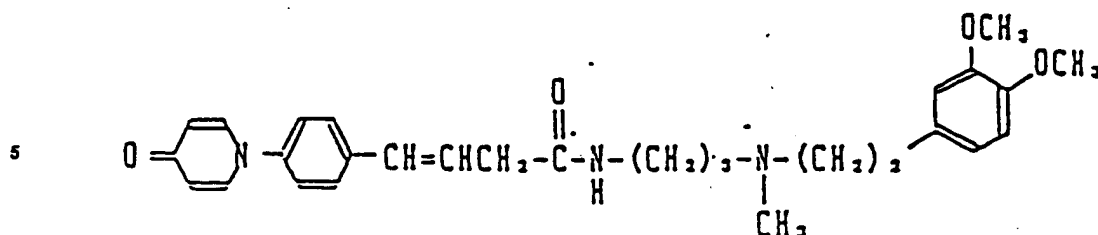
(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1,3-oxazol-5-yl)phenyl)-3-butenamide

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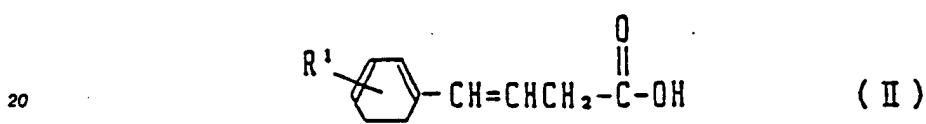
(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-pyridon-1-yl)-phenyl)-3-butenamide



Representative processes for the preparation of the compounds of the present invention will now be described.

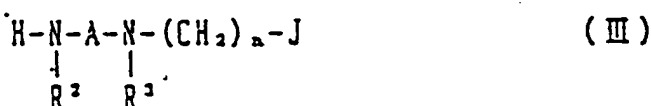
Preparation Process

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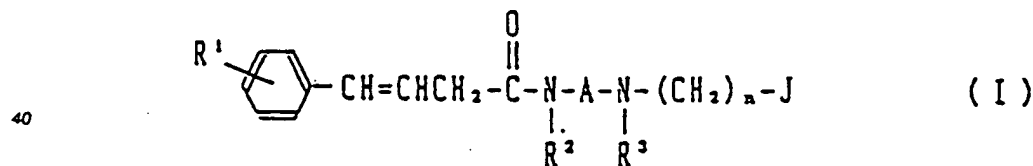
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wherein R¹, R², R³, n, A and J are each as defined above.

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Namely, the objective compound (I) can be prepared by reacting a carboxylic acid represented by the general formula (II) or a reactive derivative thereof with an amine compound represented by the general formula (III) to carry out amidation.

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The reactive derivative of the compound (II) includes acyl halides such as acyl chloride and acyl bromide; acid azides; reactive esters thereof with N-hydroxybenzotriazole or N-hydroxysuccinimide; symmetric acid anhydrides and mixed acid anhydrides thereof with alkylcarbonic acid or p-toluenesulfonic acid.

When a compound (II) is used as a free acid, it is preferable to carry out the above reaction in the presence of a condensing agent under cooling with ice or under reflux by heating. Examples of the condensing agent include dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole, ethyl chloroformate, diethyl azodicarboxylate and dipyridyl disulfide.

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The reaction may be carried out in water or an inert organic solvent by using a compound (II) or a reactive derivative thereof and a compound (III) in molar amounts which are nearly equal to each other or one of which is slightly larger than the other. Examples of the inert organic solvent include methanol, ethanol, pyridine, tetrahydrofuran, dioxane, ether, benzene, toluene, xylene, methylene chloride, dich-

loroethane, chloroform, dimethylformamide, ethyl acetate and acetonitrile.

Depending upon the kind of the reactive derivative, it is advantageous from the standpoint of the smoothness of the reaction to use a base such as diisopropylethylamine, triethylamine, pyridine, picoline, lutidine, N,N-dimethylaniline, 4-dimethylaminopyridine, potassium carbonate or sodium hydroxide.

5 The reaction temperature is not particularly limited but varies depending upon the kind of the reactive derivative. Generally, the reaction is carried out at a temperature of from -20° C to reflux temperature to obtain the objective compound.

The compound represented by the general formula (II) to be used as a starting material in the present invention can be prepared by, for example, the following process:

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(wherein X is a halogen atom
or a methanesulfonyloxy group)

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(Step 1)

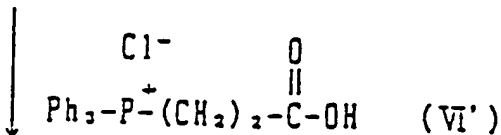


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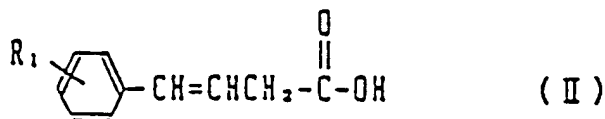


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(Step 2)



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(In the above formulas, R¹ is as defined above and Ph is a phenyl group)

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(Step 1)

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In this step, a compound represented by the general formula (V) is reacted with a compound represented by the general formula (IV) in the presence of a copper catalyst such as copper powder or copper oxide under heating to carry out an Ullmann reaction. Thus, a compound (VI) is obtained. This reaction may be carried out in the absence of any solvent or in the presence of an inert organic solvent such as nitrobenzene, dimethylformamide or pyridine, or water.

Alternatively, a compound represented by the general formula (VI) may be prepared by reacting a compound represented by the general formula (V) with a salt of a compound represented by the general formula (IV) with a metal such as lithium, sodium or potassium and subjecting the obtained intermediate to a replacement reaction or the like.

5 This reaction may be carried out in the absence of any solvent or in the presence of an inert organic solvent such as dimethylformamide, dimethylacetamide, dimethyl sulfoxide, dioxane, ether or tetrahydrofuran.

10 (Step 2)

A compound represented by the general formula (VI) is reacted with a compound represented by the general formula (VI) in the presence of potassium t-butoxide, caustic potash, caustic soda, sodium methoxide, sodium ethoxide or sodium hydride in a suitable solvent at a temperature of -78°C to a room temperature according to an ordinary process to obtain a compound (II). Examples of the solvent include ether, tetrahydrofuran, dioxane, dimethylformamide, dimethylacetamide and dimethyl sulfoxide.

Further, a compound represented by the general formula (VI) may be also prepared by the following process:

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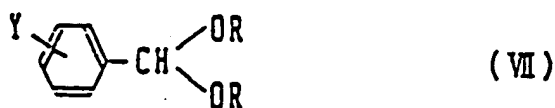
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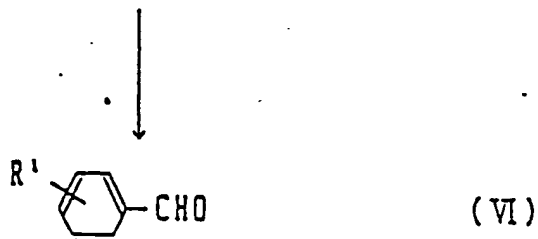
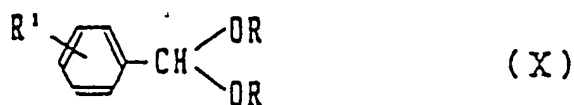
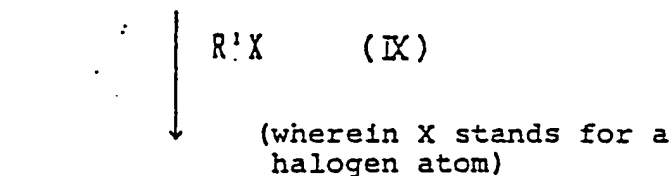
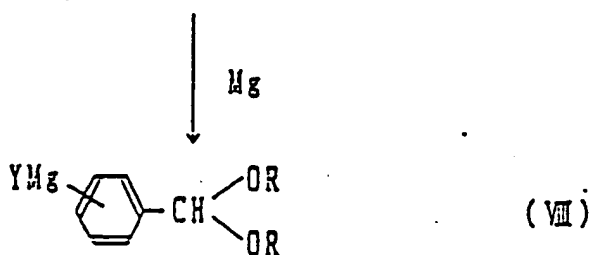
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(wherein Y stands for a halogen atom and R stands for a lower alkyl or lower alkylene group)



(In the above formulas, R¹ is as defined above)

Namely, a compound represented by the general formula (VII) is reacted with metallic magnesium under heating in a solvent such as ether or tetrahydrofuran, if necessary, in the presence of an iodine as a catalyst to obtain a Grignard reagent (VIII). This Grignard reagent is reacted with a halide represented by the formula (IX) in the presence of a metal complex catalyst at a room or elevated temperature or under reflux by heating according to an ordinary process to obtain a compound represented by the general formula (X). Examples of the catalyst include bis(1,3-diphenylphosphinopropane)nickel (II) chloride and tetrakis(triphenylphosphine)palladium. The compound represented by the general formula (X) is deacetalized with an acid to obtain a compound (VI).

The compound (III) to be used as the other starting material can be prepared by, for example, the following processes:

(Preparation Process 1)



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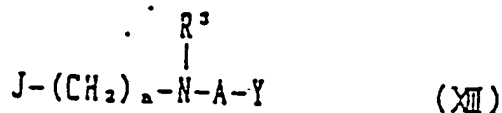
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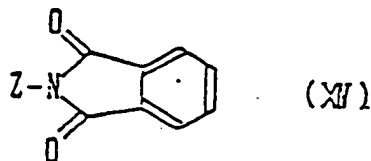
(Step 1)



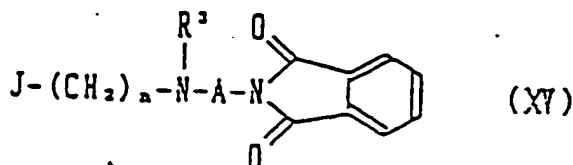
(wherein X and Y are each a leaving group such as a halogen atom or a methane-sulfonyloxy or p-toluene-sulfonyloxy group or a protected hydroxyl group such as tetrahydropyranyloxy, trimethylsiloxy, t-butyl-dimethylsiloxy or trityloxy group)



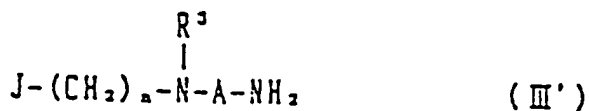
(Step 2)



(wherein Z stands for a hydrogen atom or an alkali metal)



(Step 3)

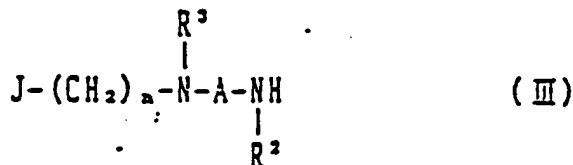


(a compound of the formula (III) wherein R^2 is a hydrogen atom)

(Step 4)

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15 (in the above formulas, R^2 , R^3 , n , A and J are each as defined above)

(Step 1)

20 In this step, a compound represented by the formula (XI) is reacted with a compound represented by the formula (XII) according to an ordinary process to obtain a compound (XIII).

More specifically, the above reaction is carried out in a suitable solvent in the presence of a base such as potassium carbonate, sodium carbonate, triethylamine or diisopropylethylamine under heating to obtain a compound (XIII). Examples of the solvent include benzene, toluene, xylene, dimethylformamide, acetonitrile, dimethyl sulfoxide, dioxane and tetrahydrofuran.

25

(Step 2)

30 When Y is a leaving group such as a halogen atom or a methanesulfonyloxy group, the compound (XIII) is reacted with an alkali metal salt of phthalimide (XIV) such as potassium or sodium salt thereof in the presence of a base such as potassium carbonate or sodium carbonate to obtain a compound (XV). On the other hand, when Y is a protected hydroxyl group such as a trityloxy or *t*-butyldimethyl-siloxy group, the compound (XIII) is freed of the protective group according to an ordinary method and subjected to the Mitsunobu reaction with phthalimide, triphenylphosphine or diethyl azodicarboxylate to obtain a compound (XV). In this case, it is preferable to use an inert solvent such as dimethyl sulfoxide, dimethylformamide, dimethylacetamide, acetonitrile or tetrahydrofuran.

35

(Step 3)

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A compound represented by formula (XV) is reacted with, for example, hydrazine monohydrate in an organic solvent such as methanol or ethanol under reflux to obtain a compound (III') (corresponding to a compound of formula (III) wherein R^2 is a hydrogen atom).

45

(Step 4)

50 A compound represented by formula (III') (corresponding to a compound of formula (III) wherein R^2 is a hydrogen atom) is reacted with an aldehyde or ketone in the presence of a catalyst such as palladium/carbon, platinum oxide or Raney nickel in a hydrogen atmosphere to carry out reductive amination. Thus, a compound represented by formula (III) is obtained.

The aldehyde and ketone to be used in this step include acetone, cyclobutanone, cyclopentanone and benzaldehyde. A solvent may be used in this step and examples thereof include methanol, ethanol, benzene, toluene, xylene, dimethylformamide, tetrahydrofuran, dioxane and ethyl acetate.

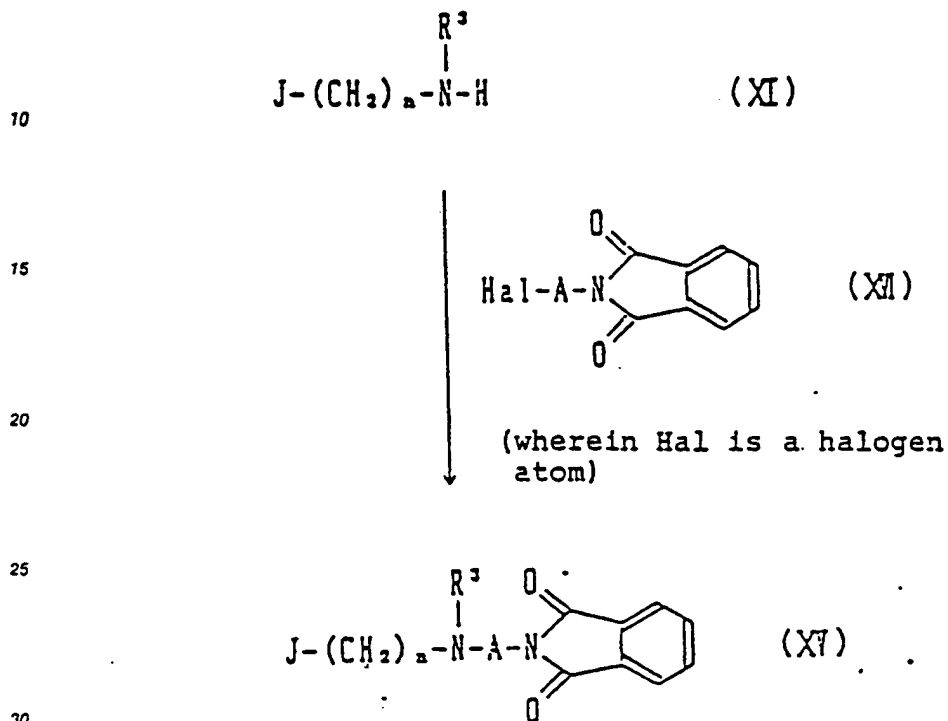
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Alternatively, a compound represented by formula (III) can be prepared by converting a compound represented by formula (III') into an amide or carbamate thereof, for example, *N*-formyl, *N*-acetyl, *N*-methoxycarbonyl or *N*-ethoxycarbonyl derivative according to an ordinary process and reducing the obtained amide or carbamate in the presence of a metal hydride complex such as lithium aluminum hydride

or boran.

This reduction may be carried out in a solvent at a room or elevated temperature or under reflux by heating and examples of the solvent include ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and diethylene glycol dimethyl ether.

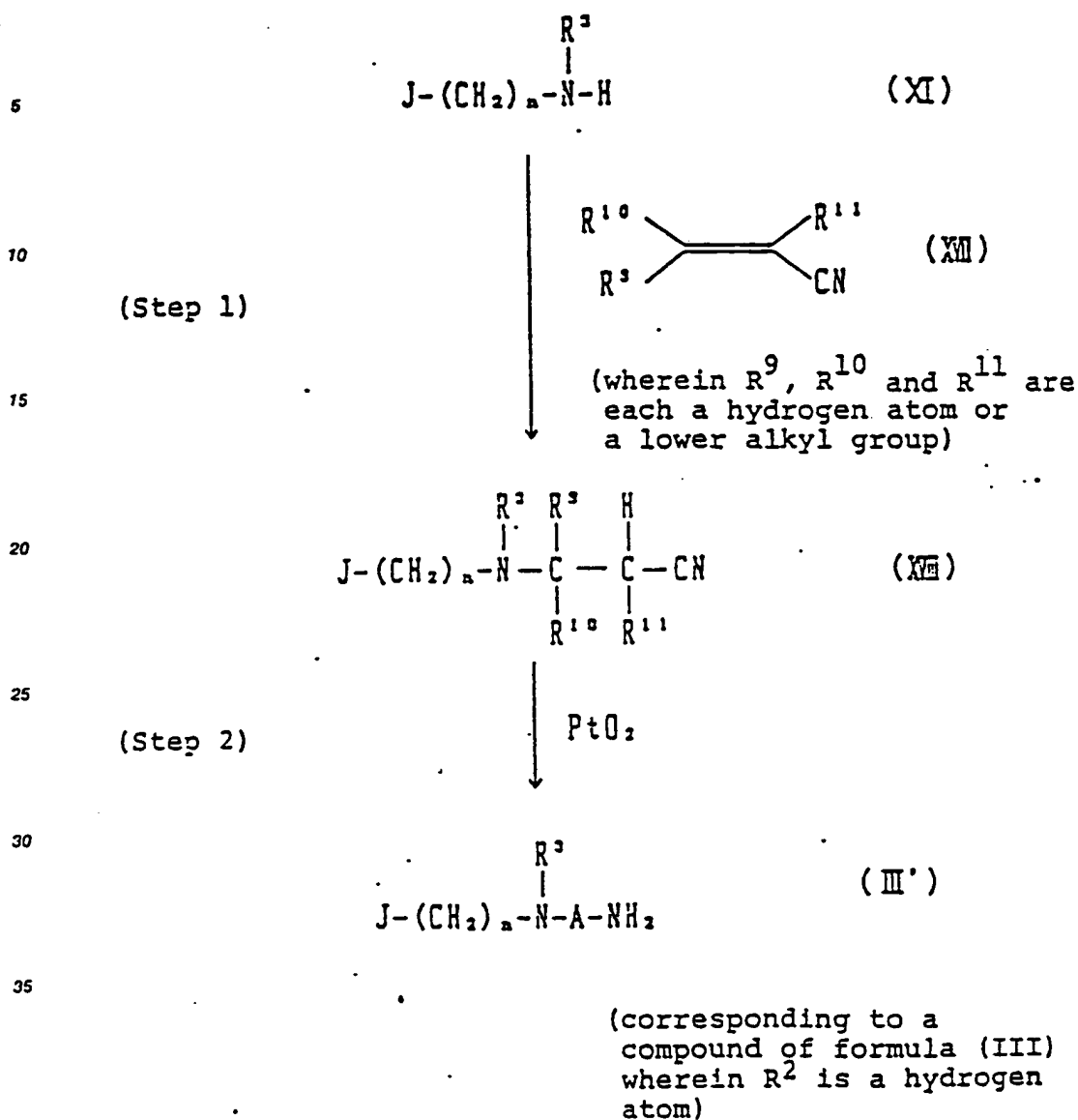
Further, a compound (XV) can be also prepared by the following process:



Namely, a compound represented by formula (XI) is reacted with a compound (XII) in the presence of a base such as potassium carbonate, sodium carbonate, caustic soda, triethylamine or diisopropylethylamine at a room or elevated temperature or under reflux by heating to obtain a compound (XV).

A suitable solvent may be used in this step and examples thereof include dimethyl sulfoxide, dimethylformamide, dimethylacetamide and acetonitrile.

(Preparation Process 2)



(Step 1)

45 A compound represented by formula (XI) is reacted with a compound represented by formula (XVII) in the absence of any solvent or in the presence of a solvent such as dichloromethane, chloroform, acetonitrile, dimethylformamide, dimethyl sulfoxide, ether, tetrahydrofuran, methanol or ethanol under heating or reflux to obtain a compound (XVIII).

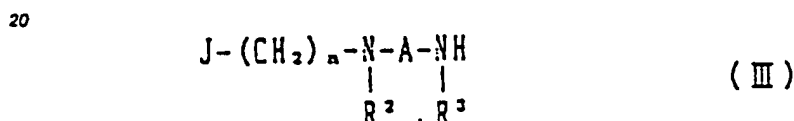
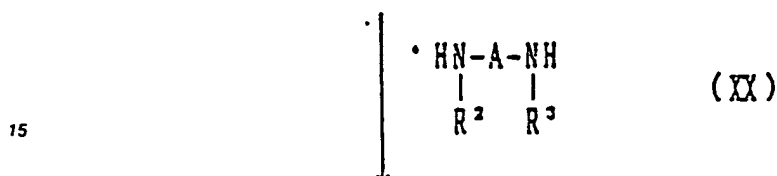
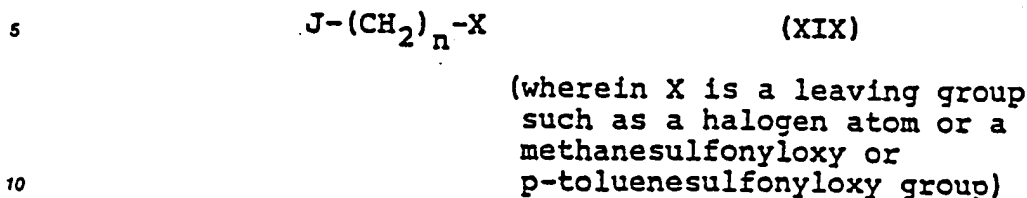
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(Step 2)

A compound represented by formula (XVIII) is hydrogenated in the presence of a catalyst such as palladium/carbon, platinum oxide or Raney nickel to obtain a compound represented by the formula (III').

55 The hydrogenation is carried out in a solvent such as methanol, ethanol, dimethylformamide or ethyl acetate under an ordinary or elevated pressure at an ordinary or elevated temperature.

(Preparation Process 3)



25 The invention further provides the pharmacological use of the compounds of the invention. A pharmacological composition of the invention comprises a pharmacologically effective amount of the butenoic or propenoic acid derivative as defined by the formula II and a pharmacologically acceptable carrier. Further here is provides a method for treating, preventing, remitting or ameliorating ischemic heart diseases by administering the butenoic or protoenic acid derivative having the formula II in a pharmacologically effective amount to a human being. The compound of the invention provides, in particular, an excellent coronary vasodilating and heart rate lowering effect.

30 Accordingly, the compound of the present invention is effective for the treatment, prevention, remission or amelioration of ischemic heart diseases such as coronary sclerosis, various angina pectoris or cardiac infarction.

35 When the compound of the present invention is to be used as a drug, it may be administered either orally or parenterally. The dose varies depending upon the degree of symptoms; the age, sex, weight and sensitivity of a patient; the method, timing and interval of administration; the properties, preparation method and kind of a drug or the kind of an active ingredient and therefore is not particularly limited. Generally, the dose is about 1 to 1000 mg, preferably about 5 to 500 mg, still preferably about 50 to 200 mg. It is generally administered at once or in 2 to 4 portions.

40 A solid drug containing the compound of the present invention for oral administration may be prepared by mixing a compound of the present invention with a filler and, if necessary, binder, disintegrator, lubricant, coloring agent or corrigent and shaping the obtained mixture into tablet, coated tablet, granule, powder or capsule.

45 Examples of the filler include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide. Examples of the binder include polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylmethylcellulose, calcium citrate, dextrin and pectin. Examples of the lubricant include magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. The coloring agent may be any one permitted to be added to a drug. The corrigent includes cacao powder, mentha herb, aromatic powder, mentha oil, borneol and powdered cinnamon bark. Of course, the tablet or granule may be coated with sugar, gelatin or the like.

50 An injection containing the compound of the present invention can be prepared by mixing a compound of the present invention as a principal agent with pH adjustor, buffer, suspending agent, solubilizing agent, stabilizer, tonicity agent or preservative and treating the obtained mixture by an ordinary process to obtain an intravenous, subcutaneous or intramuscular injection. If necessary, the injection may be freeze-dried by an ordinary method.

55 Examples of the suspending agent include methylcellulose, Polysorbate 80, hydroxyethylcellulose,

acacia, tragacanth powder, sodium carboxymethylcellulose and polyoxyethylene sorbitan monolaurate.

Examples of the solubilizing agent include polyoxyethylene hardened castor oil, Polysorbate 80, nicotinamide, polyoxymethylene sorbitan monolaurate, macrogol and ethyl ester of castor oil fatty acid.

Examples of the stabilizer include sodium sulfite, sodium metasilicate and ether, while those of the preservative include methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol and chlorocresol.

A compound represented by the formula (XIX) is reacted with a compound (XX) in the presence of a base such as potassium carbonate, sodium carbonate, caustic soda, triethylamine or diisopropylethylamine at a room or enhanced temperature or under reflux to obtain a compound (III).

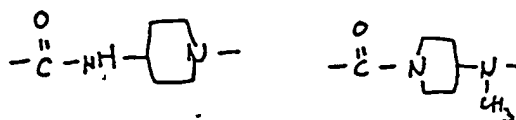
A suitable solvent may be used in this process and examples of the solvent include dimethyl sulfoxide, dimethylformamide, dimethylacetamide and acetonitrile.

Embodiment (II)

In the embodiment (II), it is preferable that G is the phenyl having R15 and R16, R15 and R16 each are hydrogen, a halogen, cyano, a lower alkoxy, -NR7R8, R7 and R8 each being hydrogen or a lower alkyl, an alkylthio or an alkanoylamino, or R15 and R16 may form a cyclic ring together with oxygen and the two adjacent carbon atoms, R11 and R12 each are hydrogen, m is zero or 1, X is oxygen, R2 is hydrogen or may form a cyclic ring together with R12, A is an alkylene having 1 to 3 carbon atoms, R3 is a lower alkyl, n is an integer of 1 to 3, J is the phenyl having R4, R5 and R6, R4, R5 and R6 each are hydrogen or a lower alkyl.

It is also preferable that J is m-dimethoxy-phenyl or m,p-dimethoxy-phenyl.

When R2 or R3 forms a heterocyclic ring with A, the following two are preferable:



Also in the embodiments (II), preferable groups for the lower alkyl, the lower alkoxy and the cycloalkyl are defined in the same way as shown in the embodiments (I).

It is more preferable that R15 and R16 are a halogen such as fluorine, cyano, a lower alkoxy such as methoxy and ethoxy, a mono- or di-lower alkylamino such as dimethylamino, an alkylthio such as methylthio, an alkanoylamino such as CH3CONH- and methylenedioxy.

It is preferable that R11 and R12 are hydrogen at the same time.

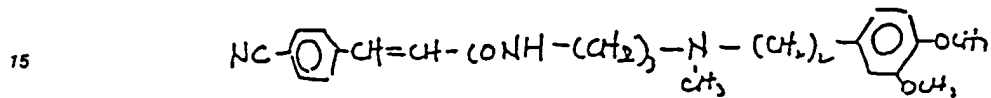
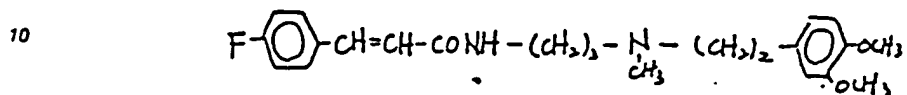
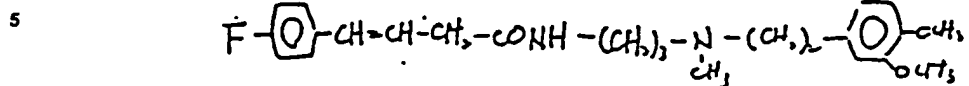
Preferable groups of -NR2-A-NR3- are defined in the same way as shown in the embodiment (I).

Most preferable compounds are:

- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-fluorophenyl)-3-buteneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-3-(4-fluorophenyl)propeneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-3-(4-cyanophenyl)propeneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(3,4-(methylenedioxy)-phenyl)-3-buteneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-cyanophenyl)-3-buteneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(3,4-dimethoxyphenyl)-3-buteneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(dimethylamino)phenyl)-3-buteneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(methylthio)phenyl)-3-buteneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-chlorophenyl)-3-buteneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-methoxyphenyl)-3-buteneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(acetamino)phenyl)-3-buteneamide,
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-3-(4-fluorobenzylidene)-2-pyrrolidinone and
- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-3-(4-cyanobenzylidene)-2-

pyrrolidinone.

The above shown compounds are defined by the following formulae, respectively.



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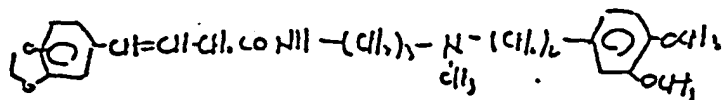
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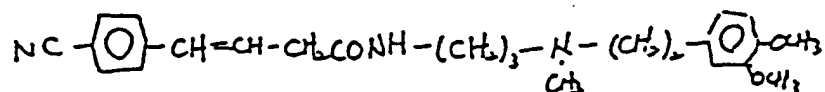
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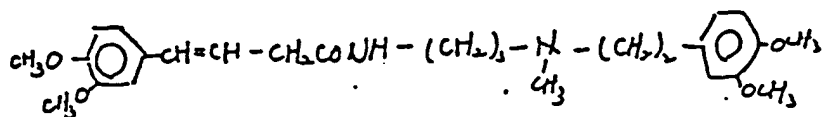
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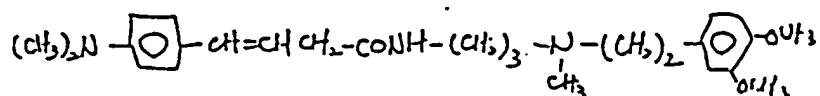
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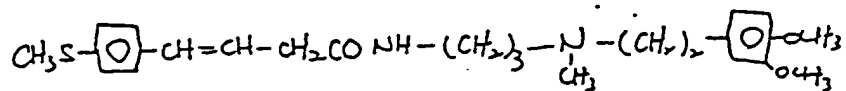
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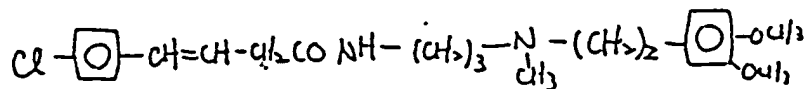
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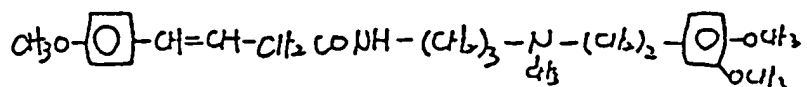
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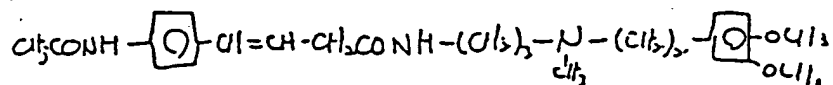
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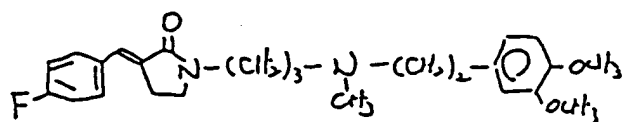
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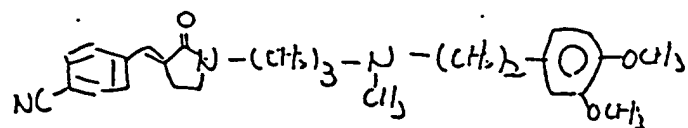
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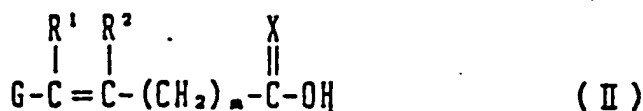
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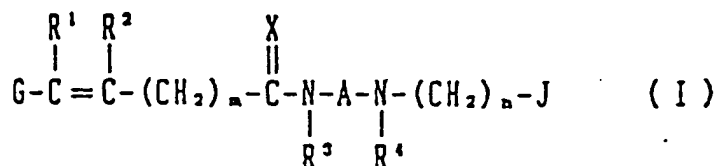
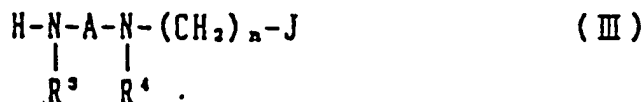
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Typical preparation methods for the compounds according to the present invention are explained below.

55 Preparation method :



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where R^1 , R^2 , R^3 , R^4 , X , m , n , G , A and J in each of the formulae have the same meanings as described above.

That is, the aimed compound (I) can be obtained by amidizing a carboxylic acid or thiocarboxylic acid represented by the general formula (II) or the reactive derivative thereof with an amino compound represented by the general formula (III).

As the reactive derivative of the compound (II), there can be mentioned active esters with acid halide such as acid chloride or acid bromide, acid azide, *N*-hydroxybenzotriazole, or *n*-hydroxysuccinic imide, mixed acid anhydride with symmetric acid anhydride, alkyl carbonic acid, *p*-toluene sulfonic acid or phosphoric acid ester, etc.

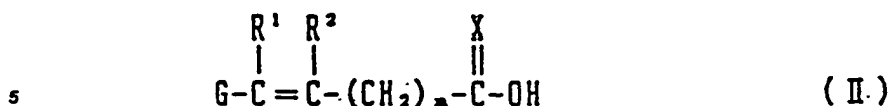
When free carboxylic acid is used as the compound (II), it is preferred to react under the presence of a condensating agent such as dicyclohexyl carbodiimide, 1,1'-carbonyl diimidazole, chloroformate, diethyl azodicarboxylate, dipyridyldisulfide, etc. under ice cooling or heat-refluxing.

The reaction was carried out by using a compound (II) or the reactive derivative thereof and a compound (III) substantially in an equi-molar ratio or at a slight excess molar ratio of one of them, in a solvent such as water or an organic solvent inert to the reaction, for example, methanol, ethanol, pyridine, tetrahydrofuran, dioxane, ether, benzene, toluene, xylene, methylene chloride, dichloroethane, chloroform, dimethylformamide, methylene chloride, ethyl acetate and acetonitrile.

Depending on the kind of the reactive derivative, it may be some time advantageous to add a base such as diisopropyl ethylamine, triethylamine, pyridine, picoline, lutidine, *N,N*-dimethylaniline, 4-dimethylaminopyridine, potassium carbonate or sodium hydroxide upon reaction in view of smooth proceeding of the reaction.

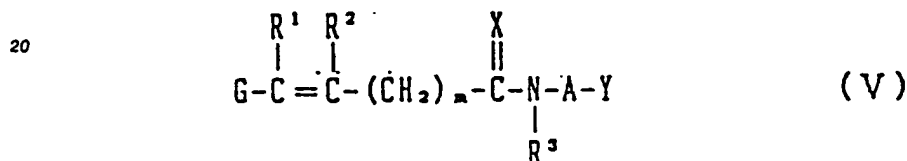
The reaction temperature varies depending on the kind of the reactive derivative and has no particular restriction, and the aimed compound can usually be obtained by reaction at a temperature from -20°C to heat-refluxing temperature.

Further, the compound (I) can also be prepared by the following method.

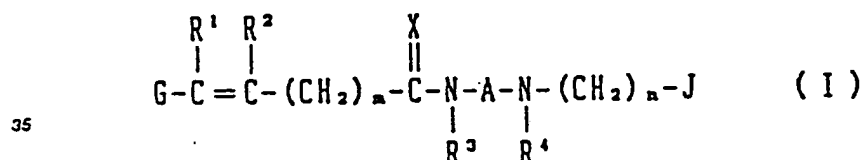


(First step)

(where Y represents a splitting group such as halogen atom, methane sulfonyloxy or p-toluene sulfonyloxy)



(Second step)



where R^1 , R^2 , R^3 , R^4 , X, m, n, G, A and J in each of the formulae have the same meanings as described above.

(First Step)

In this the step, the compound (V) is formed by amidizing a carboxylic acid or thlocarboxylic acid represented by the general formula (II) or the reactive derivative thereof by the reaction with an amino compound represented by the general formula (IV).

As the reactive derivative of the compound (II), there can be mentioned active esters with acid halide such as acid chloride or acid bromide, acid azide, N-hydroxybenzotriazole or n-hydroxysuccin imide, mixed acid anhydride with symmetric acid anhydride, alkyl carbonic acid, p-toluene sulfonic acid or phosphoric acid ester, etc.

When free carboxylic acid is used as the compound (II), it is preferred to react under the presence of a condensating agent such as dicyclohexyl carbodiimide, 1,1'-carbonyl diimidazole, chloroformate, diethyl azodicarboxylate, dipyridyldisulfide, etc. under ice cooling or heat refluxing.

The reaction was carried out by using a compound (II) or the reactive derivative thereof and a compound (III) substantially in an equi-molar ratio or at a slight excess molar ratio of one of them, in a solvent such as water or an organic solvent inert to the reaction, for example, methanol, ethanol, pyridine, tetrahydrofuran, dioxane, ether, benzene, toluene, xylene, methylene chloride, dichloroethane, chloroform,

dimethylformamide, methylene chloride, ethyl acetate and acetonitrile.

Depending on the kind of the reactive derivative, it may be some time advantageous to add a base such as diisopropyl ethylamine, triethylamine, pyridine, picoline, lutidine, N,N-dimethylaniline, 4-dimethylaminopyridine, potassium carbonate or sodium hydroxide upon reaction, in view of smooth proceeding of the reaction.

The reaction temperature varies depending on the kind of the reactive derivative and has no particular restriction, and the aimed compound can usually be obtained by reaction at a temperature from -20°C to heat-reflux temperature.

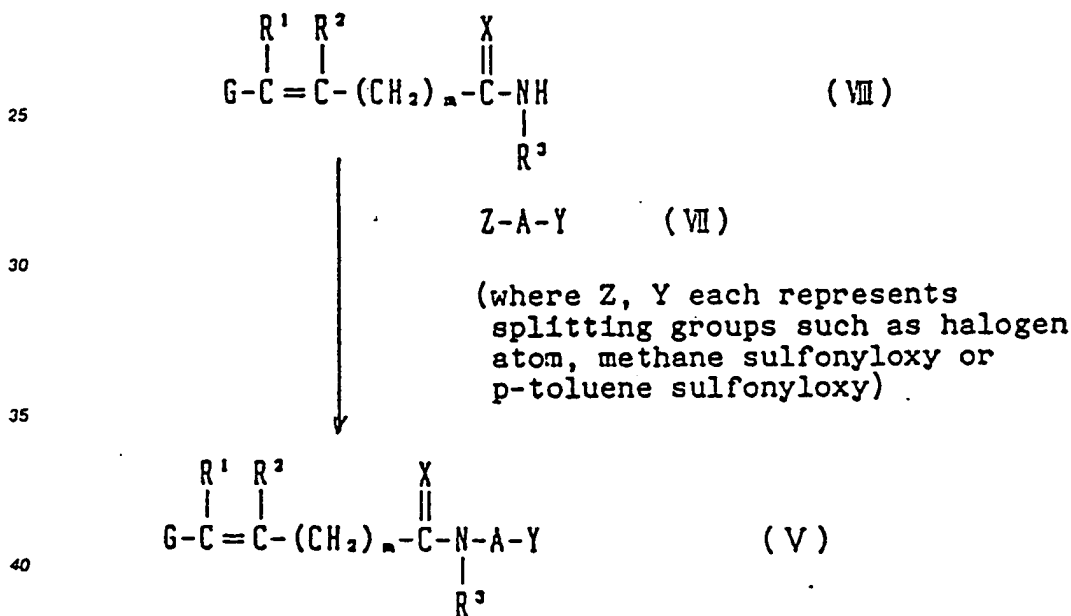
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(Second Step)

In this step, the aimed compound (I) is formed by reacting a compound represented by the general formula (V) with a compound represented by the general formula (VI) by a customary method.

15 That is, the compound (I) is formed by reacting a compound represented by the formula (V) with a compound (VI) at a temperature from a room temperature to a refluxing temperature under the presence of a base such as potassium carbonate, sodium carbonate, triethylamine and diisopropyl ethylamine.

In this case, solvent such as benzene, toluene, xylene, dimethylsulfoxide, dimethylformamide, dimethylacetamide and acetonitrile can be used.

20 The compound (V) can also be formed by the following method.



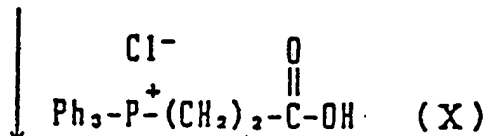
45 where $R^1, R^2, R^3, R^4, X, m, n, G, A$ and J in each of the formulae have the same meanings as described above providing that R^3 is not H .

That is, the compound (V) can be formed by reacting a compound represented by the general formula (VIII) and a compound represented by the general formula (VII) by a customary method at a temperature from an ice cooled temperature to a heat refluxing temperature by using a solvent, for example, ether, tetrahydrofuran, dioxane, dimethylformamide, dimethylacetamide and dimethylsulfoxide, under the presence of potassium tert-butoxide, sodium methoxide, sodium ethoxide, sodium amide, sodium hydride and potassium hydride.

Among the compounds represented by the general formula (II) used as the starting material in the present invention, those compounds in which $R^1 = R^2 = H$, $m = 1$, $X = O$ can be formed, for example, by the following method.



(First Step)



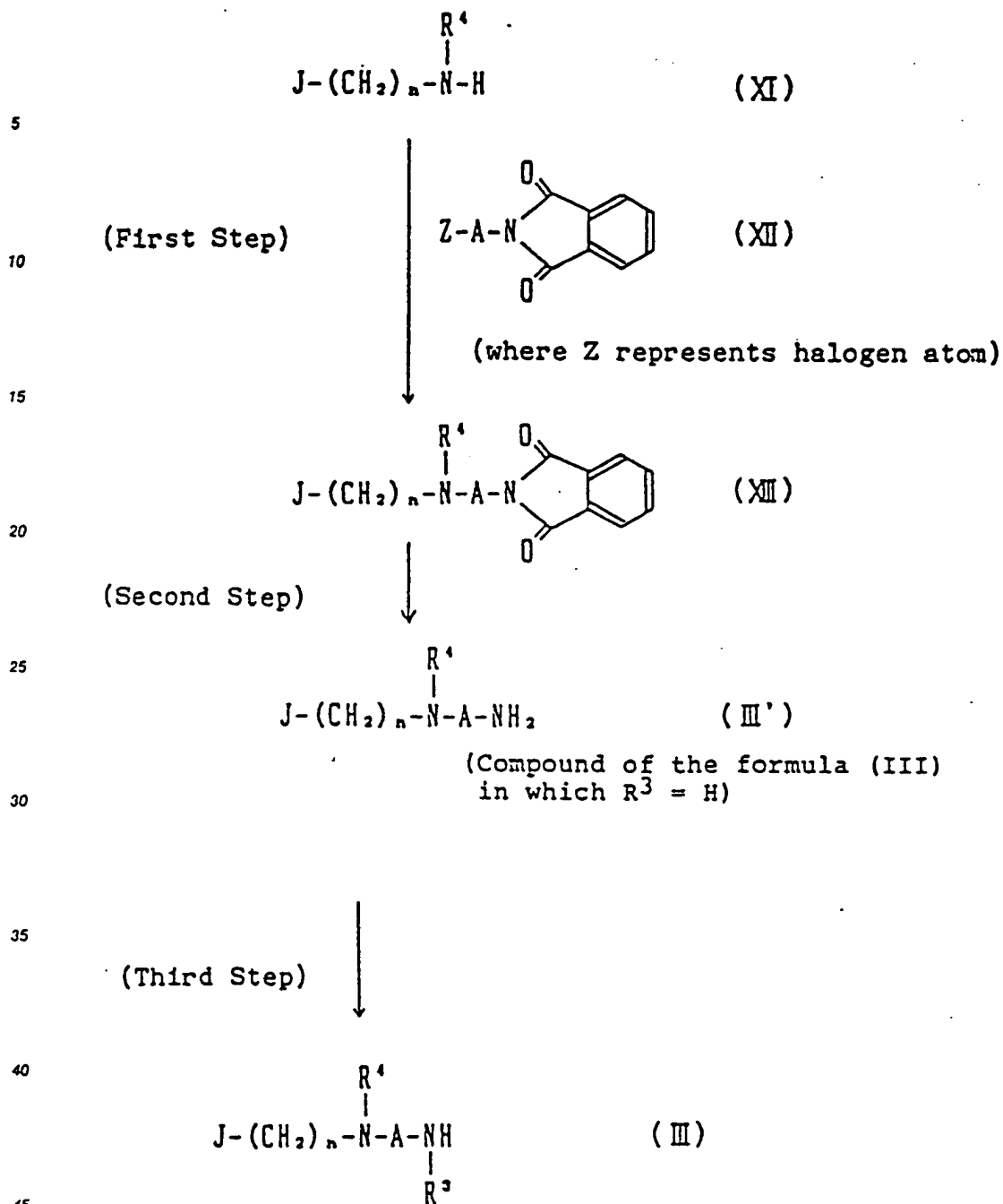
where G has the same meanings as described above and Ph represents phenyl group in each of the formulae.

(First Step)

The compound (II') can be formed by reacting a compound represented by the general formula (IX) and a compound represented by the general formula (X) by a customary method at a temperature from $-78^\circ C$ to a room temperature by using a solvent, for example, ether, tetrahydrofuran, dioxane, dimethylformamide, dimethylacetoamide or dimethylsulfoxide and under the presence of potassium t-butoxide, potassium hydroxide, sodium hydroxide, sodium methoxide, sodium ethoxide or sodium hydride.

Further, the compound (III) as the starting material can be prepared, for example, by the following preparation method.

(Preparation Method 1)



where R^3 , R^4 , n , A and J in each of the formulae have the same meanings as described above.

50 (First Step)

In this step, the compound (XIII) is formed by reacting a compound represented by the formula (XI) and a compound represented by the formula (XII) by a customary method.

Specifically, the compound (XII) is formed by reacting both of the compounds at a temperature from a room temperature to a heat refluxing temperature by using a solvent, for example, benzene, toluene, xylene, 55 dimethylformamide, acetonitrile, dimethylsulfoxide, dioxane and tetrahydrofuran and under the presence of a base, for example, potassium carbonate, sodium carbonate, triethylamine and diisopropylethylamine.

(Second Step)

A compound (III'), where $R^3 = H$ in the formula (III), can be formed by reacting a compound represented by the formula (XII), for example, with a hydrazine monohydrate under heat reflux in the presence of an organic solvent such as methanol or ethanol.

(Third Step)

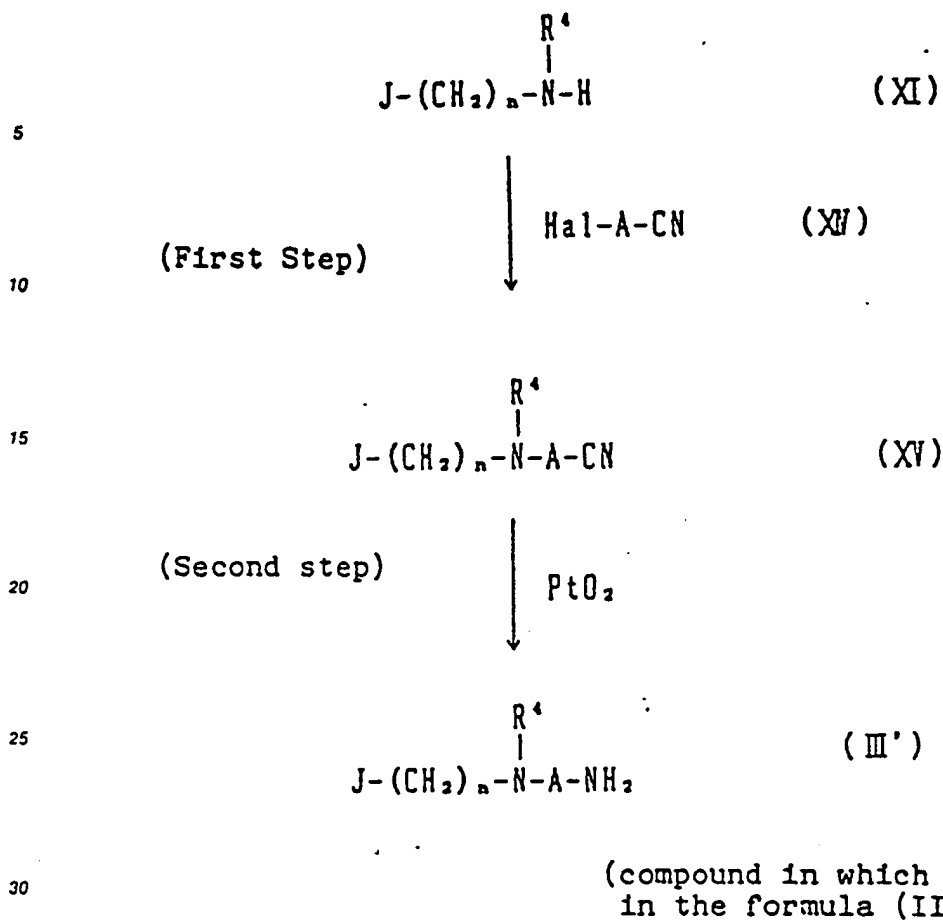
A compound represented by the formula (III) can be formed by conducting amidizing reduction between a compound represented by the formula (III'), in which $R^3 = H$ in the formula (III), and an aldehyde or ketone by using a catalyst such as palladium-carbon, platinum oxide, Raney nickel, etc. in a hydrogen atmosphere.

In this case, acetone, cyclobutanone, cyclopentanone or benzaldehyde can be used as the aldehyde or ketone. As the reaction solvent, there can be used methanol, ethanol, benzene, toluene, xylene, dimethylformamide, tetrahydrofuran, dioxane and ethyl acetate.

As an alternative method, a compound represented by the formulae (III) can be formed by converting a compound represented by the formula (III') into an acidamide or carbamate, for example, N-formyl, N-acetyl, N-methoxycarbonyl or N-ethoxycarbonyl by a customary method, which is then reduced with a metal hydrogen complex compound, for example, aluminum lithium hydride or borane.

The reductive reaction is conducted at a temperature from a room temperature to a heat refluxing temperature by using a solvent such as ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, etc.

(Preparation Method 2)



35 where R^4 , n , A and J in each of the formulae have the same meanings as described above and Hal represents a halogen atom.

(First Step)

40 The compound (XV) can be prepared by reacting a compound represented by the formula (XI) and a compound represented by a formula (XIV) at a temperature from a room temperature to a heat refluxing temperature without using solvent or under the presence of a solvent such as dichloromethane, chloroform, acetonitrile, dimethylformamide, dimethylsulfoxide, ether, tetrahydrofuran, methanol, ethanol, etc.

45 (Second Step)

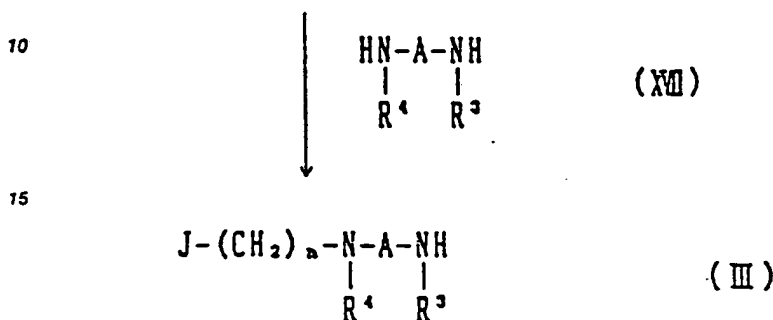
The compound represented by the formula (III') can be prepared by subjecting a compound represented by the formula (XV) to a hydrogenating reaction by using a catalyst such as palladium-carbon, platinum oxide or Raney nickel.

50 In this case, the reaction is conducted under the pressure from a normal pressure to an elevated pressure and at a temperature from a normal temperature to an elevated temperature while using a solvent, for example, methanol, ethanol, dimethylformamide and ethyl acetate.

55 (Preparation method 3)



(where Y represents a splitting group such as a halogen atom, methane sulfonyloxy or p-toluene sulfonyloxy)



where R^3 , R^4 , n , A , J in each of the formulae have the same meanings as described above.

The compound (III) can be prepared by reacting a compound represented by the formula (XVI) with a compound (XVII) at a temperature from a room temperature to a heat refluxing temperature under the presence of a base such as potassium carbonate, sodium carbonate, sodium hydroxide, triethylamine and diisopropylethylamine.

As the reaction solvent used in this case, there can be used, for example, those solvents such as dimethylsulfoxide, dimethylformamide, dimethylacetamide or acetonitrile.

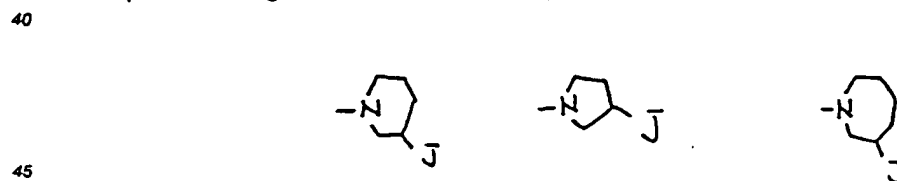
Embodiment (III)

This is defined with the above shown formula (III).

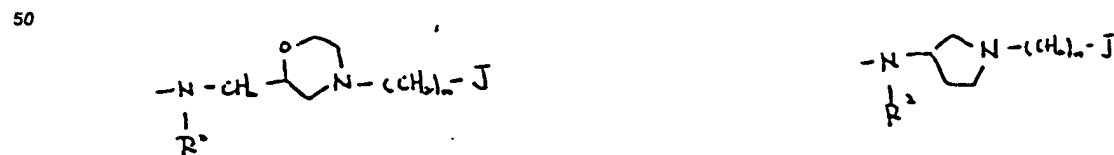
It is preferable that W is azomethyne or sulfur ($-S-$) and R_2 is hydrogen.

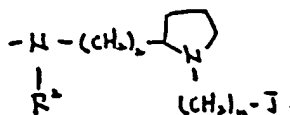
The heterocyclic ring for R_{31} has the same preferable groups as shown for R_1 . In addition, there is included a heteroaryl having a nitrogen(s) such as pyridazinyl, pyrazinyl, 1,2-dihydro-2-oxopyridyl, an enantiomeric isomer thereof, 2,3-dihydro-3-oxopyridazinyl and an enantiomeric isomer thereof. A heterocyclic ring having nitrogen and sulfur includes thiazolyl, isothiazolyl.

A preferable ring formed from R_3 , N and $-(CH_2)_n$ includes:

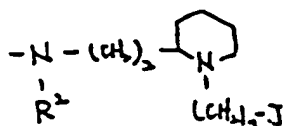


A preferable ring formed from R_3 , A and N includes:

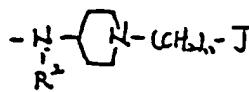
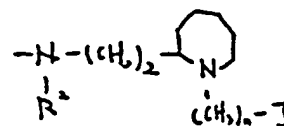




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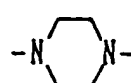


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The lower alkyl, the lower alkoxy and the cycloalkyl are defined for their preferable groups in the same way as shown in the embodiment (I).

The ring formed from R₂, R₃, N, A and N includes:

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Preferable groups for R₄, R₅ and R₆ are defined in the same way as shown in the embodiment (I).

Most preferable compounds are:

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(2-pyrazinyl)phenyl)-3-buteneamide,

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(1,3-thiazol-4-yl)-phenyl)-3-buteneamide,

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(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(2-methyl-1,3-thiazol-4-yl)phenyl)-3-buteneamide,

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(3-(1H-imidazol-1-yl)-thiophene-5-yl)-3-buteneamide,

35

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(2-(1H-imidazol-1-yl)-thiophene-5-yl)-3-buteneamide,

(E)-N-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-3-pyrrolidinyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-buteneamide,

(E)-N-(2-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-2-pyrrolidinyloxy)-4-(4-(1H-imidazol-1-yl)phenyl)-3-buteneamide,

40

(E)-N-(2-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-2-piperidinoethoxy)-4-(4-(1H-imidazol-1-yl)phenyl)-3-buteneamide, (E)-N-(3-((N'-(2-(3,5-dimethoxyphenyl)ethyl)-N'-methyl)amino)-2-hydroxypropyl)-4-(4-(1H-imidazol-1-yl)-phenyl)-3-buteneamide and

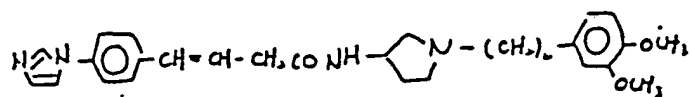
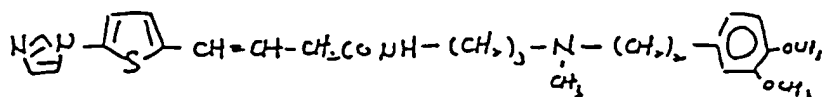
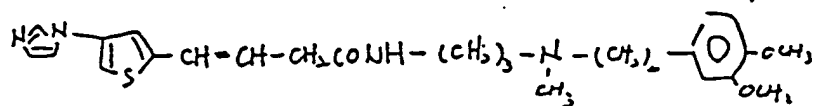
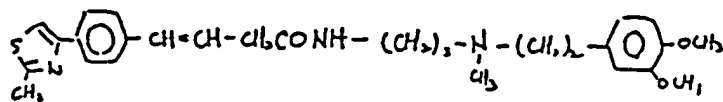
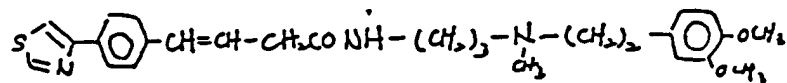
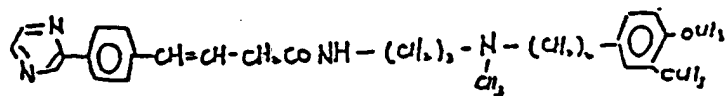
(E)-N-(1-(2-(3,4-dimethoxyphenyl)ethyl)-4-piperidinyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-buteneamide.

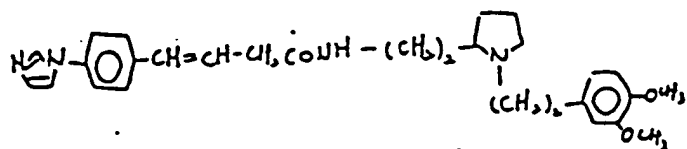
The above listed compounds have the following formulae, respectively.

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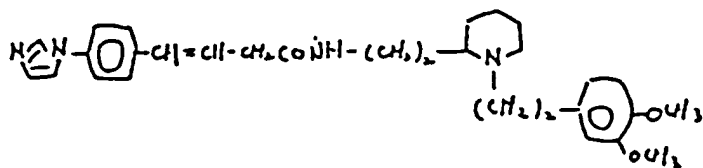
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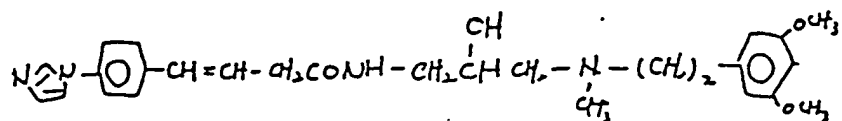




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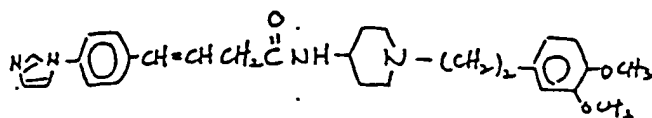


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Preparation methods for the embodiments III are described below in reference to examples in which W is vinylene. The methods apply to the other groups than vinylene for W.

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Preparation method :

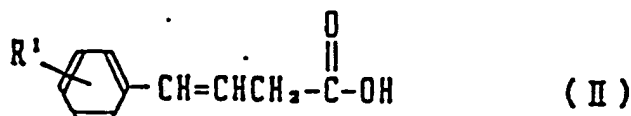
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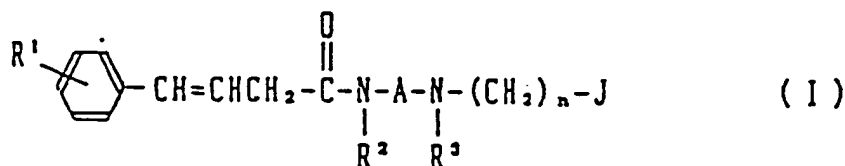
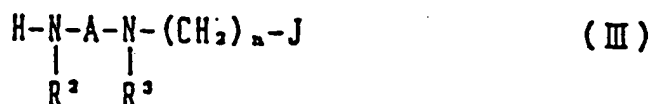
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+



where R^1 , R^2 , R^3 , n , and J in each of the formulae have the same meanings as described above.

That is, the aimed compound (I) can be obtained by amidizing a carboxylic acid represented by the general formula (II) or the reactive derivative thereof with an amino compound represented by the general formula (III).

As the reactive derivative of the compound (II), there can be mentioned active esters with acid halide such as acid chloride or acid bromide, acid azide, N-hydroxybenzotriazole or n-hydroxysuccinic imide, mixed acid anhydride with symmetric acid anhydride, alkyl carbonic acid, p-toluene sulfonic acid or phosphoric acid ester, etc.

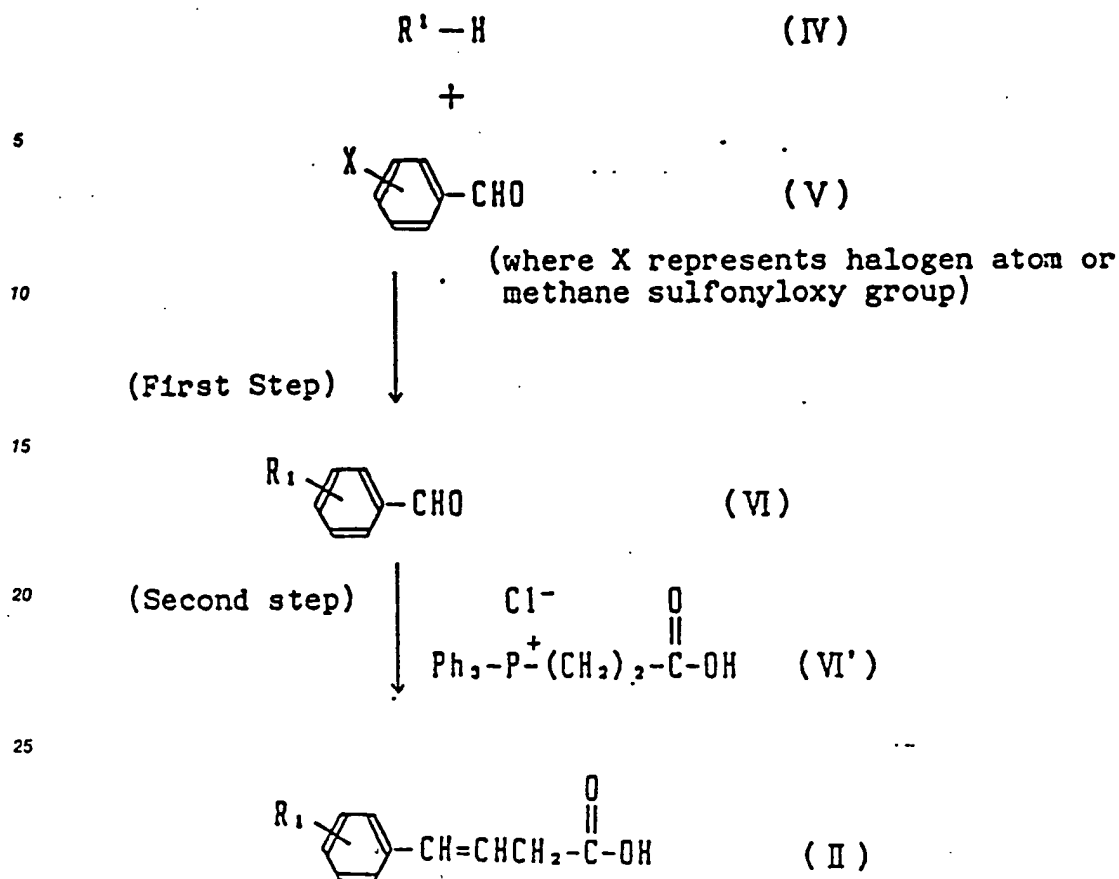
When free carboxylic acid is used as the compound (II), it is preferred to react under the presence of a condensating agent such as dicyclohexyl carbodiimide, 1,1'-carbonyl diimidazole, chloroformate, diethyl azodicarboxylate, dipyridyldisulfide, etc. under ice cooling or heat-refluxing.

The reaction was carried out by using a compound (II) or the reactive derivative thereof and a compound (III) substantially in an equi-molar ratio or at a slight excess molar ratio of one of them, in a solvent such as water or an organic solvent inert to the reaction, for example, methanol, ethanol, pyridine, tetrahydrofuran, dioxane, ether, benzene, toluene, xylene, methylene chloride, dichloroethane, chloroform, dimethylformamide, methylene chloride, ethyl acetate and acetonitrile.

Depending on the kind of the reactive derivative, it may be some time advantageous to add a base such as diisopropyl ethylamine, triethylamine, pyridine, picoline, lutidine, N,N-dimethylaniline, 4-dimethylaminopyridine, potassium carbonate or sodium hydroxide upon reaction in view of smooth proceeding of the reaction.

The reaction temperature varies depending on the kind of the reactive derivative and has no particular restriction, and the aimed compound can usually be obtained by reaction at a temperature from -20°C to heat-refluxing temperature.

The compound represented by the general formula (II) used as the starting material in the present invention can be prepared, for example, by the following method.



where R' in each of the formulae has the same meanings as described above and Ph represents phenyl group.

(First Step)

In this the step, the compound (VI) is formed by subjecting a compound represented by the general formula (V) and a compound represented by the general formula (IV) to Ullmann type reaction under heating using a copper catalyst such as copper powder or copper oxide.

In this case, the reaction can be carried out without solvent or by using those inert organic solvents not relevant to the reaction, for example nitrobenzene, dimethylformamide, pyridine or water.

As another method of forming the compound represented by the general formula (VI), there can be mentioned a method of reacting a compound represented by the general formula (V) with a compound represented by the general formula (IV) after being converted into a metal salt such as of lithium, sodium or potassium and then preparing the compound (VI) by substituting reaction, etc.

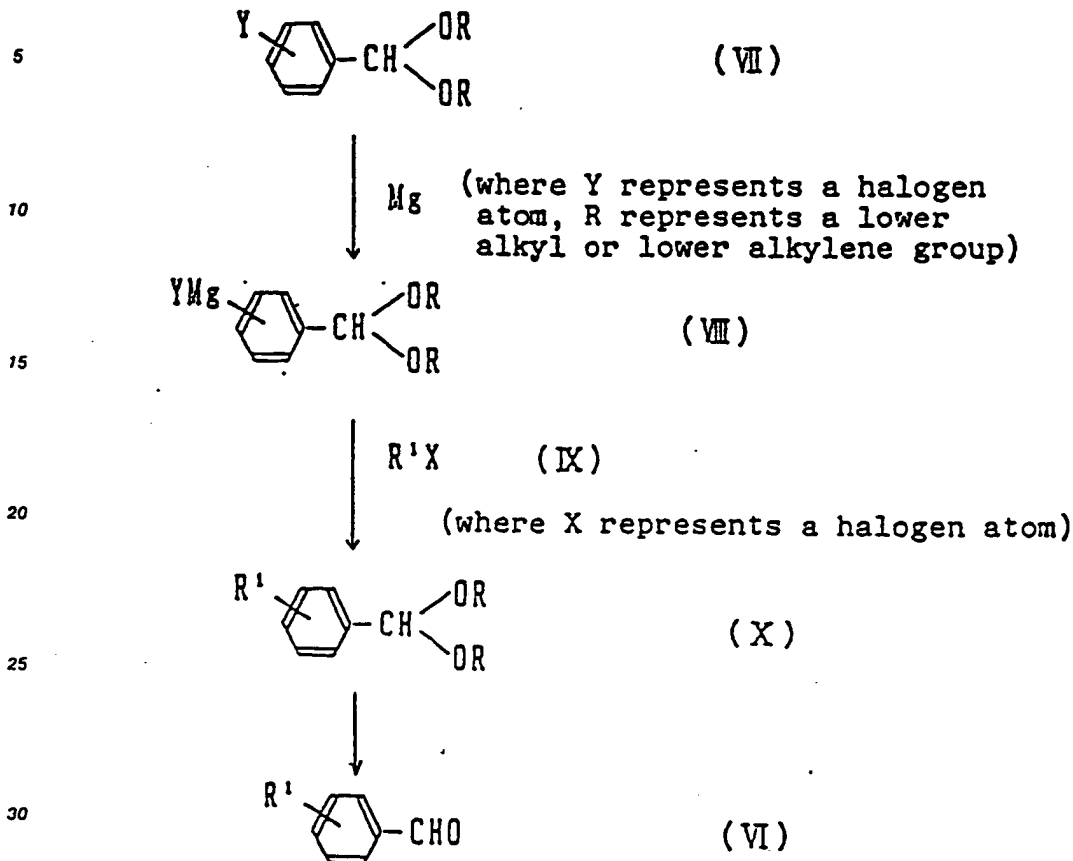
The reaction can be carried out without using solvent or by using those inert organic solvents not relevant to the reaction, for example, dimethylformamide, dimethylacetamide, dimethylsulfoxide, dioxane, ether and tetrahydrofuran.

(Second Step)

The compound (II) can be formed by reacting a compound represented by the general formula (VI) and a compound represented by the general formula (VI') by a customary method at a temperature from -78°C to a room temperature by using a solvent, for example, ether, tetrahydrofuran, dioxane, dimethylformamide, dimethylacetamide and dimethylsulfoxide, under the presence of potassium tert-butoxide, sodium methox-

ide, sodium ethoxide, sodium amide, sodium hydride and potassium hydride.

Another method of forming the compound represented by the general formula (VI) is shown below :

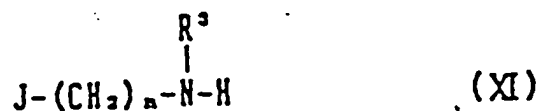


35 where R¹ has the same meanings as described above in each of the formulae.

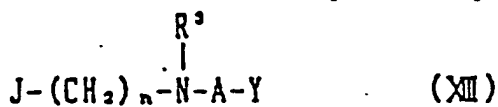
That is, a compound represented by the general formula (VII) is heated together with metal magnesium under the presence of a solvent such as ether or tetrahydrofuran and with addition of iodine as a catalyst if required, to prepare a Grignard reagent (VIII). Then, it is reacted with a halide represented by the formula (IX) with addition of a metal complex as a catalyst, for example, bis(1,3-diphenylphosphinopropane) nickel (II) chloride or tetrakis(triphenylphosphine) palladium by a customary method at a temperature from a room temperature to a heat refluxing temperature to prepare a compound represented by the general formula (X). Then, the compound is deacetalized with an acid to obtain a compound represented by the general formula (VI).

45 Further, the compound (III) as the starting material can be prepared, for example, by the following preparation method.

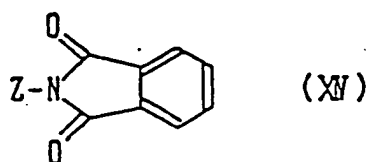
(Preparation Method 1)



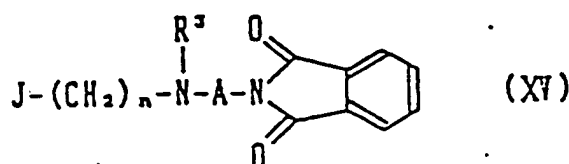
(where X, Y each represents a splitting group such as a halogen atom, methane sulfonyloxy, p-toluene sulfonyloxy, or a protected hydroxy group such as tetrahydropyranyloxy, trimethyloxy, tert-butyldimethylsiloxy or trityloxy)



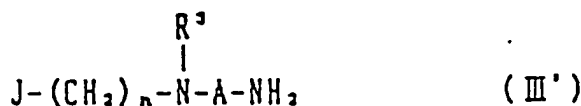
(Second Step)



(where Z represents hydrogen atom or alkali metal)

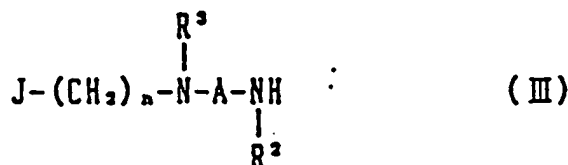


(Third Step)



(Compound of the formula (III) in which $\text{R}^2 = \text{H}$)

(Fourth step)



where R^2 , R^3 , n , A and J in each of the formulae have the same meanings as described above.

(First Step)

In this step, the compound (XIII) is formed by reacting a compound represented by the formula (XI) and a compound represented by the formula (XII) by a customary method.

Specifically, the compound (XIII) is formed by reacting both of the compounds at a temperature from a room temperature to a heat refluxing temperature by using a solvent, for example, benzene, toluene, xylene, dimethylformamide, acetonitrile, dimethylsulfoxide, dioxane and tetrahydrofuran and under the presence of a base, for example, potassium carbonate, sodium carbonate, triethylamine and diisopropylethylamine.

(Second Step)

In a case where Y represents a stripping group, for example, a halogen atom or methane sulfonyloxy, a compound represented by the formula (XIII) is reacted with an alkali metal salt of phthalimide represented by the formula (XIV) such as potassium phthalimide or sodium phthalimide under the presence of a base such as potassium carbonate or sodium carbonate, to form a compound represented by the formula (XV). When Y is a protected hydroxy, for example trityloxy or tert-butyldimethylsiloxy, the protecting group is removed by a conventional method and then Mitsunobu reaction using phthalimide, trimethylphosphine and diethylazodicarboxylate is conducted to prepare a compound of the formula (XV). In this case, an inert solvent not relevant to the reaction, preferably, dimethylsulfoxide, dimethylformamide, dimethylacetamide, acetonitrile, tetrahydrofuran, etc. are used as the solvent.

(Third Step)

A compound (III'), where $\text{R}^3 = \text{H}$ in the formula (III), can be formed by reacting a compound represented by the formula (XV), for example, with a hydrazine monohydrate under heat reflux in the presence of an organic solvent such as methanol or ethanol.

(Fourth Step)

A compound represented by the formula (III) can be formed by conducting amidizing reduction between a compound represented by the formula (III'), in which $\text{R}^3 = \text{H}$ in the formula (III), and an aldehyde or ketone by using a catalyst such as palladium-carbon, platinum oxide, Raney nickel, etc. in a hydrogen atmosphere.

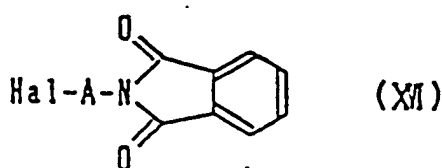
In this case, acetone, cyclobutanone, cyclopentanone or benzaldehyde can be used as the aldehyde or ketone. As the reaction solvent, there can be used methanol, ethanol, benzene, toluene, xylene, dimethylformamide, tetrahydrofuran, dioxane and ethyl acetate.

As an alternative method, a compound represented by the formula (III) can be formed by converting a compound represented by the formula (III') into an acidamide or carbamate, for example, N-formyl, N-acetyl, N-methoxycarbonyl or N-ethoxycarbonyl by a customary method, which is then reduced with a metal hydrogen complex compound, for example, aluminum lithium hydride or borane.

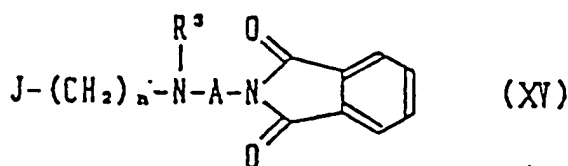
The reductive reaction is conducted at a temperature from a room temperature to a heat refluxing

temperature by using a solvent such as ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, etc.

The compound (XV) can also be obtained by the following method.



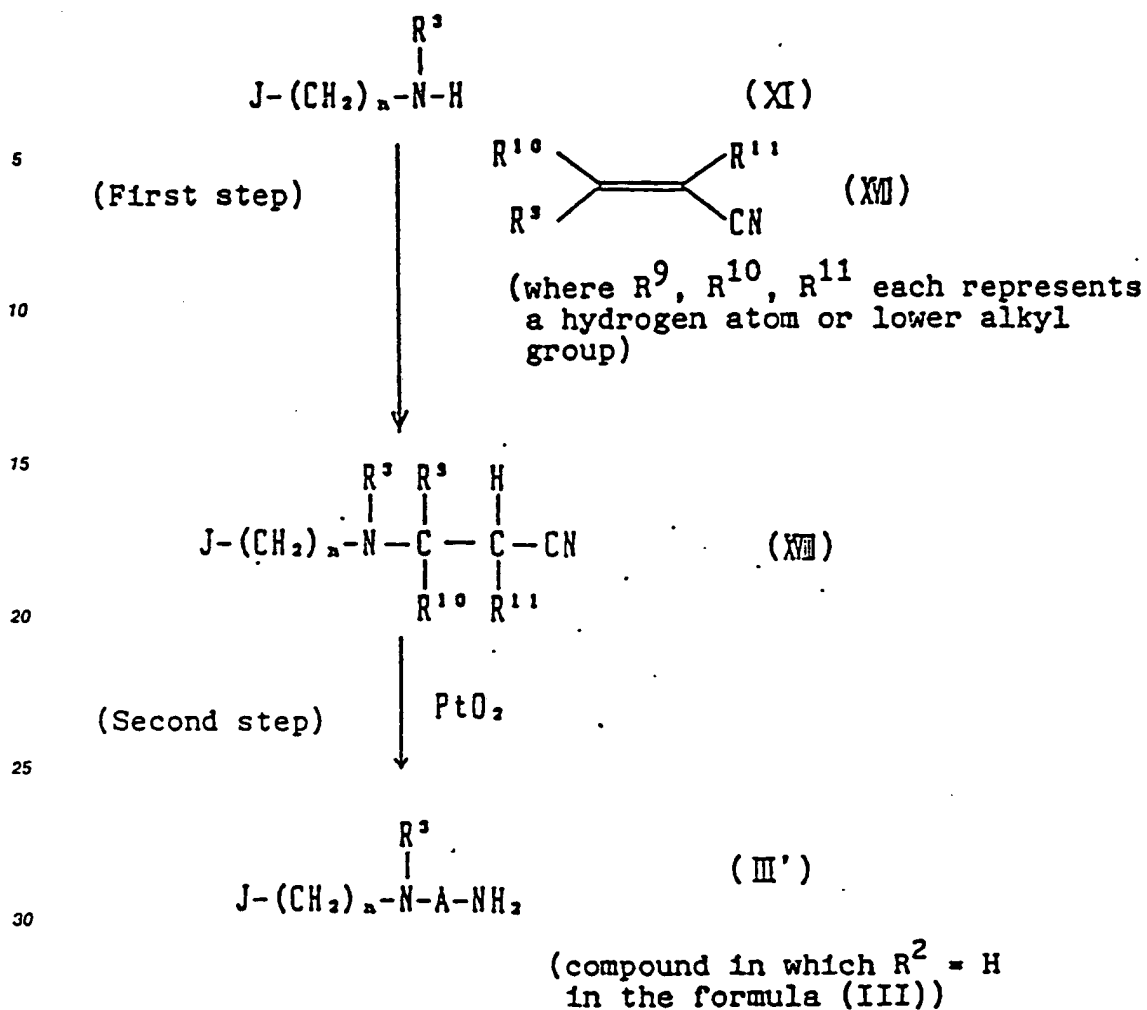
(where Hal represents a halogen atom)



That is, a compound of the formula (XV) is formed by reacting a compound represented by the formula (XI) with a compound represented by the formula (XVI) under the presence of a base, for example, potassium carbonate, sodium carbonate, sodium hydroxide, triethylamine and diisopropylisoethylamine at a temperature from a room temperature to a refluxing temperature.

In this case, those solvents, for example, dimethylsulfoxide, dimethylformamide, dimethylacetamide and acetonitrile can be used as the solvent.

(Preparation Method 2)



(First Step)

The compound (XVIII) can be formed by reacting a compound represented by the formula (XI) and a compound represented by the formula (XVII) at a temperature from a room temperature to a heat refluxing temperature without using solvent or under the presence of a solvent such as dichloromethane, chloroform, acetonitrile, dimethylformamide, dimethylsulfoxide, ether, tetrahydrofuran, methanol, ethanol, etc.

(Second Step)

The compound represented by the formula (III') can be formed by subjecting a compound represented by the formula (XVIII) to a hydrogenating reaction by using a catalyst such as palladium-carbon, platinum oxide or Raney nickel.

In this case, the reaction is conducted under the pressure from a normal pressure to an elevated pressure and at a temperature from a normal temperature to an elevated temperature while using a solvent, for example, methanol, ethanol, dimethylformamide and ethyl acetate.

(Preparation method 3)



(where X represents a splitting group such as a halogen atom, methane sulfonyloxy or p-toluene sulfonyloxy)

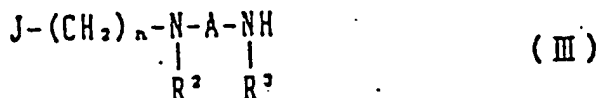
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The compound (III) can be formed by reacting a compound represented by the formula (XIX) with a compound of the formula (XX) at a temperature from a room temperature to a heat refluxing temperature under the presence of a base such as potassium carbonate, sodium carbonate, sodium hydroxide, triethylamine and diisopropylethylamine.

As the reaction solvent used in this case, there can be used, for example, those solvents such as dimethylsulfoxide, dimethylformamide, dimethylacetamide or acetonitrile.

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(pharmacological test)

Pharmacological tests were conducted for the compounds of the invention including the embodiments I, II and III, in view of (1) the effect upon cardiac muscle extirpated from guinea pig, (2) the heart rate lowering and coronary bloodflow increasing effects upon anesthetized thoracotomized dog and (3) the toxicity.

The test compounds, A to M of I, A to J of II and A to E of III are listed below.

40 compounds A to M of I

Compound A (compound of Example 1)

45 (E)-N-{3-[(N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)-phenyl)-3-butenamide

Compound B (compound of Example 2)

50 (E)-N-{3-[(N'-(2-(3,5-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)-phenyl)-3-butenamide

Compound C (compound of Example 3)

55 (E)-N-{3-[(N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)butyl]-4-(4-(1H-imidazol-1-yl)-phenyl)-3-butenamide

Compound D (compound of Example 19)

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(3-pyridyl)phenyl)-3-butenamide

Compound E (compound of Example 23)

- 5 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-pyrrol-1-yl)-phenyl)-3-butenamide

Compound F (compound of Example 26)

- 10 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-benzimidazol-1-yl)phenyl)-3-butenamide

Compound G (compound of Example 9)

- 15 (E)-N-[3-((N'-(2-Phenylethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

Compound H (compound of Example 10)

- 20 (E)-N-[3-((N'-(2-(3,4,5-Trimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)-phenyl)-3-butenamide

Compound I (compound of Example 29)

- 25 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(4-(1H)-pyridon-1-yl)phenyl)-3-butenamide

Compound J (compound of Example 7)

- 30 (E)-N-[3-((N'-(2-(3-Methoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)-phenyl)-3-butenamide

Compound K (compound of Example 13)

- 35 (E)-N-[3-((N'-(2-(3,4-Methylenedioxyphenyl)-ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

Compound L (compound of Example 18)

- 40 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(4-methyl-1H-imidazol-1-yl)-phenyl)-3-butenamide

Compound M (compound of Example 25)

- 45 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-butenamide

compounds A to J of II

- 50 A:

(E)-N-[3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-fluorophenyl)-3-buteneamide dihydrochloride,

- 55 B:

(E)-N-[3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(3,4-methylenedioxy)-phenyl)-3-buteneamide dihydrochloride,

C:

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-3-(4-fluorophenyl)-propeneamide,

5 D:

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-3-(4-cyanophenyl)-propeneamide,

E:

10

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-3-(4-fluorobenzylidene)-2-pyrrolidinone,

F:

15 (E)-N-(3-((N'-(2-(4-methoxyphenyl)ethyl)-N'-allyl)amino)propyl)-3-(4-fluorophenyl)-propeneamide,

G:

(E)-N-(3-((N'-(3-(3,4-dimethoxyphenyl)pyrrolidin-1-yl)propyl)-3-(4-fluorophenyl)-propeneamide,

20

H:

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-methoxyphenyl)-3-buteneamide,

25 I:

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(3,4,5-trimethoxyphenyl)-3-buteneamide,

30 J:

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-N-cyclopentyl-4-(4-cyano-phenyl)-3-buteneamide,

35 compounds A to E of III

A:

40 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(1,3-thiazol-4-yl)-phenyl)-3-buteneamide,

B:

45 (E)-N-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-3-pyrrolidino)-4-(4-(1H-imidazol-1-yl)phenyl)-3-buteneamide,

C:

50 (E)-N-(2-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-2-pyrrolidino)ethyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-buteneamide,

D:

55 (E)-N-(3-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(1H-imidazol-1-yl)-thiophene-2-yl)-3-buteneamide,

E:

(E)-N-(3-((N'-(3-(3,4-dimethoxyphenyl)-2-propyl)-N'-methyl)amino)propyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-buteneamide.

Now, Pharmacological Experiment Examples will be described to illustrate the effect of the compound of the present invention in more detail.

55

Pharmacological Experiment Example

Experimental Example 1

Effect upon cardiac muscle extirpated from guinea pig

15 The effect of the compound (test compound) of the present invention upon cardiac muscle was examined by using a male guinea pig having a weight of 300 to 500 g. Namely, a right atrium was extirpated from a male guinea pig and perfused with a Krebs-Henseleit solution to count its spontaneous contractions with a cardiometer. The logarithm of the concentration of a test compound at which the heart rate was reduced by 30% is shown in Table 1.

20

Table 1(I)

25

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Effect upon cardiac muscle extirpated from guinea pig	
Test compound	-log EC ₃₀
Compound A	6.3
Compound B	5.9
Compound C	6.0
Compound D	6.8
Compound E	6.6
Compound F	6.1
Compound G	6.1
Compound H	5.5

Table 1(II)

45

50

test compound		-log EC ₃₀
compound	A	6.6
	B	6.8
	C	6.0
	D	6.1
	E	6.3

55

Table 1(III)

test compound		-log EC30
compound	A	6.4
	B	6.5
	C	6.2
	E	5.7

Experimental Example 2

Heart rate lowering and coronary bloodflow increasing effects upon anesthetized thoracotomized dog

The chest of a grown-up mongrel was opened under enflurane inhalation anesthesia. The blood flow of the coronary artery was determined by setting a probe of an electromagnetic bloodflowmeter at its left circumflexbranch, while the heart rate was determined by triggering the wave form of the pressure in its left ventricle and counting it with a tachometer.

The intravenous administration of a test compound (in a dose of 0.3 mg per kg of the weight of the anesthetized mongrel) was carried out by using a catheter inserted into its femoral artery.

The effect of increasing the bloodflow of the circumflex branch of the left coronary artery or the heart rate lowering effect was evaluated based on the difference between the bloodflow or the heart rate after the administration and that before the administration according to the following criteria. The results are shown in Table 2 by a symbol (+).

Table 2(I)

Heart rate lowering and coronary bloodflow increasing effects on anesthetized thoracotomized dog		
Test compound	Heart rate (HR)	Coronary bloodflow (CBF)
Compound A	+++	+
Compound B	++	+++
Compound C	+	+++
Compound I	±	+++
Compound J	+	+
Compound K	++	+
Compound L	+	+
Compound M	+	+

Table 2(II)

test compound		heart rate (HR)
compound	A	++
	B	+++
	D	+++
	F	+++
	G	++
	H	++
	I	+
	J	+

Table 2(III)

test compound		heart rate (HR)	coronary bloodflow (CBF)
compound	A	+++	±
	B	+	+
	D	++	+

Note) Symbols "+", "++", "+++" and "±" each stand for a rate of reduction in heart rate or a rate of increase in coronary bloodflow as shown in Table 3.

Table 3

Rate of reduction in HR		Rate of increase in CBF	
±	0%	±	0%
+	1 - 10%	+	1 - 100%
++	11 - 20%	++	101 - 200%
+++	21 - 30%	+++	201 - 300%

Experimental Example 3

Toxicity test

The representative compounds of the present invention were examined by an ordinary acute toxicity test (intravenous injection) using a mouse to obtain the results shown in Table 4.

Table 4

Test compound	LD ₅₀ (mg/kg, iv)
Compound A	92
Compound B	81
Compound C	92
Compound I	77
Compound J	77
Compound L	92
Compound M	120

(examples of the compounds)

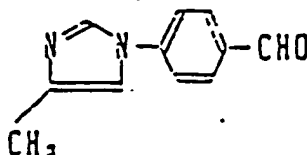
The invention will be below illustrated in reference to preparation or manufacturing examples to produce starting materials for the compounds of the invention and examples of the compounds of the invention I, II and III. They are listed below.

	I	II	III
preparation examples or manufacturing examples	1-14	1-6	1-25
examples or working examples	1-36	1-120	1-20

Examples of the compound I

Preparative Example 1

4-(4-Methyl-1H-imidazol-1-yl)benzaldehyde



4.20 g of sodium hydride (a 60% suspension thereof in a mineral oil) was suspended in 150 ml of dimethylformamide to obtain a suspension. 8.62 g of 4-methylimidazol was added to the suspension at a room temperature under stirring in portions. After one hour, 12.4 g of 4-fluorobenzaldehyde was added to the obtained mixture. The obtained mixture was stirred for 4 hours and poured into ice-water. The obtained mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate and distilled under a reduced pressure to remove the solvent. The obtained residue was purified by silica gel column chromatography (solvent: chloroform/methanol (50 : 1)) to obtain a solid product. This solid product was washed with ether to obtain 2.67 g of the title compound as a pale yellow powder (yield: 14%).

* m.p. (°C) : 85.0 to 85.5

• elemental analysis: as $C_{11}H_{10}N_2O$

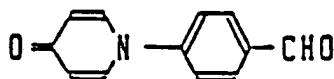
	C	H	N
calculated (%)	70.95	5.41	15.05
found (%)	71.17	5.51	15.13

• NMR($CDCl_3$) δ :

2.29(3H,d,J = 1.5Hz), 7.04(1H,m), 7.3 – 7.5(2H,m), 7.7 – 8.1(3H,m), 9.96(1H,s)

In a similar manner to the one described above, the following compound was prepared (yield: 55%).

• 4-(4-(1H)-Pyridon-1-yl)benzaldehyde



• m.p. ($^{\circ}C$) : 228 to 230

• elemental analysis: as $C_{12}H_9NO_2$

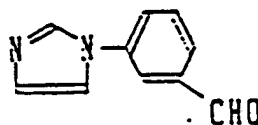
	C	H	N
calculated (%)	72.35	4.55	7.03
found (%)	72.58	4.64	7.04

• (DMSO- d_6) δ :

6.1 – 6.4(2H,m), 7.6 – 7.9(2H,m), 7.9 – 8.2(4H,m), 10.05(1H,s)

Preparative Example 2

• 3-(1H-Imidazol-1-yl)benzaldehyde



A mixture comprising 9.25 g of 3-bromobenzaldehyde, 20.4 g of imidazole, 0.31 g of copper powder and 50 ml of water was heated under reflux in a nitrogen atmosphere for 3 days, followed by the addition of aqueous ammonia. The obtained mixture was extracted with chloroform. The extract was purified by silica gel column chromatography (solvent: methylene chloride/methanol) to obtain 4.61 g of the title compound as a pale yellow crystal (yield: 54%).

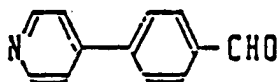
• m.p. ($^{\circ}C$): 76.0 to 77.0

• elemental analysis: as $C_{10}H_8N_2O$

	C	H	N
calculated (%)	69.75	4.68	16.27
found (%)	69.80	4.83	16.61

• NMR($CDCl_3$) δ :

7.20(1H,bs), 7.31(1H,m), 7.5-7.7(2H,m), 7.7-8.0(3H,m), 10.02(1H,s)

Preparative Example 34-(4-Pyridyl)benzaldehyde

A solution of 6.93 g of 4-bromobenzaldehyde dimethyl acetal in 40 ml of tetrahydrofuran was dropwise added to a mixture comprising 0.80 g of magnesium powder, a catalytic amount of iodine and 10 ml of tetrahydrofuran under stirring at a temperature in the bulk of 40 to 50 °C in a nitrogen atmosphere to prepare a Grignard reagent. This Grignard reagent was dropwise added to a solution of 4.46 g of 4-bromopyridine and 0.4 g of bis(1,3-diphenylphosphinopropane)nickel (II) chloride in 100 ml of tetrahydrofuran at a room temperature in a nitrogen atmosphere. The obtained mixture was refluxed for 4 hours and allowed to cool to a room temperature, followed by the addition of water. The obtained mixture was distilled to remove the tetrahydrofuran. Ethyl acetate was added to the residue. The obtained mixture was extracted with dilute hydrochloric acid thrice. The extracts were combined, allowed to stand for a short time, made alkaline with concentrated aqueous ammonia and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and distilled to remove the solvent. The residue was purified by silica gel column chromatography (solvent: chloroform/methanol) to obtain 3.28 g of the title compound as a pale yellow crystal (yield: 64%).

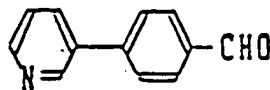
• m.p. (°C) : 89.5 to 90

• elemental analysis: as C ₁₂ H ₉ NO			
	C	H	N
calculated (%)	78.67	4.95	7.65
found (%)	78.77	5.12	7.57

• NMR(CDCl₃) δ :

7.50-7.62(2H,m), 7.75-7.93(2H,m), 7.96-8.16(2H,m), 8.70-8.84(2H,m), 10.14(1H,s)

In a similar manner to the one described in Preparative Example 3, the following compounds were prepared:

4-(3-Pyridyl)benzaldehyde

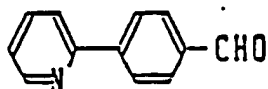
• m.p. (°C) : 53.5 to 54.5

* elemental analysis: as C₁₂H₉NO

	C	H	N
calculated (%)	78.67	4.95	7.65
found (%)	78.57	5.06	7.56

* NMR(CDCl₃) δ :

7.44(1H,ddd,J = 7.2Hz,4.7Hz,1.0Hz), 7.8 -8.2(5H,m), 8.75(1H,m), 8.94(1H,m), 10.12(1H,s)

* 4-(2-Pyridyl)benzaldehyde

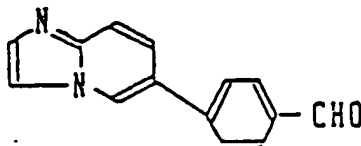
* m.p. (°C) : 48.0 to 48.5

* elemental analysis: as C₁₂H₉NO

	C	H	N
calculated (%)	78.67	4.95	7.65
found (%)	78.50	5.08	7.57

* NMR(CDCl₃) δ :

7.22(1H,m), 7.8 -7.5(2H,m), 7.90(2H,d,J = 8.3Hz), 8.08(2H,d,J = 8.3 Hz), 8.65(1H,d,J = 4.4Hz), 9.98(1H,s)

* 4-(Imidazo[1,2-a]pyridin-6-yl)benzaldehyde

* m.p. (°C) : 138.5 to 139.5

* elemental analysis: as C₁₄H₁₀N₂O

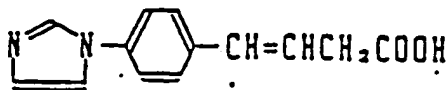
	C	H	N
calculated (%)	75.67	4.51	12.61
found (%)	75.58	4.67	12.68

* NMR(CDCl₃) δ :

7.42(1H,dd,J = 9.0Hz, 2.5Hz), 7.55 -7.80(5H,m), 7.84-8.04(2H,m), 8.15(1H,m), 9.98(1H,s)

Preparative Example 4

(E)-4-[4-(1H-imidazol-1-yl)phenyl]-3-butenolic acid



5

5.45 g of 4-(1H-imidazol-1-yl)benzaldehyde and 12.93 g of β -carboxyethyltriphenylphosphonium chloride were suspended in 70 ml of tetrahydrofuran. The obtained suspension was cooled to -50°C and vigorously stirred. 30 ml of a solution of 7.83 g of potassium t-butoxide in tetrahydrofuran was gradually added dropwise to the resulting suspension. The temperature of the obtained mixture was gradually raised to 0°C . After one hour, ice-water was added to the mixture. The obtained mixture was washed with ether. The pH of the aqueous layer was adjusted with concentrated hydrochloric acid to about 4 to precipitate a solid. This solid was recovered by filtration and washed with water and methanol to obtain 5.44 g of the title compound as a pale yellow powder (yield: 75%).

15 \bullet m.p. ($^{\circ}\text{C}$) : 212 to 213.5

\bullet elemental analysis: as $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$			
	C	H	N
calculated (%)	68.41	5.30	12.27
found (%)	68.51	5.42	12.08

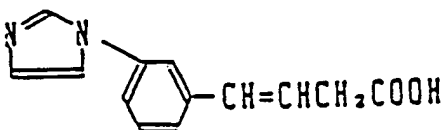
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\bullet NMR(DMSO- d_6) δ ;

25 3.21(2H,d,J=5.7Hz), 6.33(1H,dt,J=5.7Hz,15.8Hz), 6.57(1H,d,J=15.8Hz), 7.10(1H, s), 7.3 -7.7(4H,m), 7.72-(1H,s), 8.25(1H,s)

In a similar manner to the one described above, the following compounds were prepared:

30 \circ (E)-4-[3-(1H-imidazol-1-yl)phenyl]-3-butenoic acid



35

40 \bullet m.p. ($^{\circ}\text{C}$) : 148.5 to 150.0

\bullet elemental analysis: as $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$			
	C	H	N
calculated (%)	68.41	5.30	12.27
found (%)	68.23	5.39	12.34

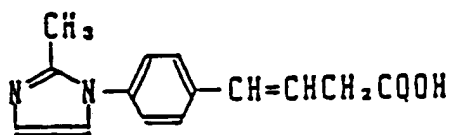
45

\bullet NMR(DMSO- d_6) δ ;

50 3.22(2H,d,J=5.4Hz), 6.4 -6.6(2H,m), 7.07(1H,s), 7.3 -7.6(3H,m), 7.66(1H,s), 7.73(1H,s), 8.24(1H,s)

\circ (E)-4-[4-(2-Methyl-1H-imidazol-1-yl)phenyl]-3-butenoic acid

55



• m.p. (°C) : 237 to 240 (dec.)

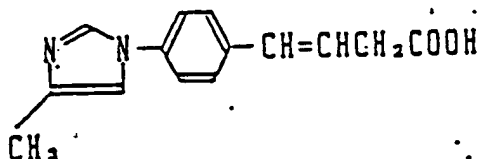
• elemental analysis: as $C_{14}H_{14}N_2O_2$

	C	H	N
calculated (%)	69.40	5.82	11.57
found (%)	69.57	6.05	11.45

• NMR(DMSO- d_6) δ :

2.30(3H,d,J = 0.9Hz), 3.22(2H,d,J = 6.2Hz), 6.37(1H,dt,J = 6.2Hz,16.3Hz), 6.61(1H,d,J = 16.3Hz), 6.92(1H,m), 7.25(1H,m), 7.3-7.4(2H,m), 7.4-7.6(2H,m)

◦ (E)-4-[4-(4-Methyl-1H-imidazol-1-yl)phenyl]-3-butenoic acid



• m.p. (°C) : 196 to 198

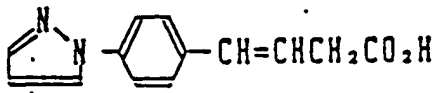
• elemental analysis: as $C_{14}H_{14}N_2O_2$

	C	H	N
calculated (%)	69.40	5.82	11.57
found (%)	69.64	5.87	11.54

• NMR(DMSO- d_6) δ :

2.17(3H,s), 3.21(2H,d,J = 6.2Hz), 6.31(1H,dt,J = 6.2Hz,16.3Hz), 6.55(1H,d,J = 16.3Hz), 7.41(1H,d,J = 0.9Hz), 7.52(4H,s), 8.13(1H,d,J = 0.9Hz)

◦ (E)-4-[4-(1H-Pyrazol-1-yl)phenyl]-3-butenoic acid

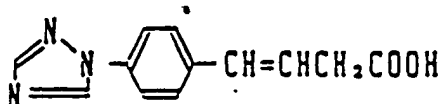


• m.p. (°C) : 140 to 142

* elemental analysis: as C ₁₃ H ₁₂ N ₂ O ₂			
	C	H	N
calculated (%)	68.41	5.30	12.27
found (%)	68.30	5.45	12.41

• NMR(CDCl₃) δ :
3.20(2H,d,J=7Hz), 6.04–6.60(3H,m), 7.2–8.1(6H,m)

• (E)-4-[4-(1,2,4-Triazol-1-yl)phenyl]-3-butenic acid

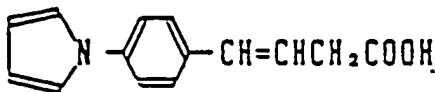


• m.p. (°C) : 217 to 218.5

* elemental analysis: as C ₁₂ H ₁₁ N ₃ O ₂			
	C	H	N
calculated (%)	62.87	4.84	18.33
found (%)	63.07	4.95	18.34

• NMR(DMSO-d₆) δ :
3.23(2H,d,J=5.7Hz), 6.36(1H,dt,J=5.7Hz,15.8Hz), 6.60(1H,d,J=15.8Hz), 7.5–7.7(2H,m), 7.7–7.9(2H,m), 8.21(1H,s), 9.28(1H,s), 12.35(1H,br)

• (E)-4-[4-(1H-Pyrrol-1-yl)phenyl]-3-butenic acid

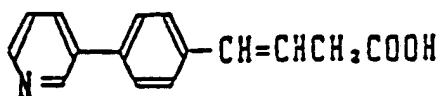


• m.p. (°C) : 191.0 to 192.0

* elemental analysis: as C ₁₄ H ₁₃ NO ₂			
	C	H	N
calculated (%)	73.99	5.77	6.16
found (%)	74.30	5.93	6.10

• NMR(CDCl₃) δ :
3.17(2H,d,J=5.8Hz), 6.04–6.62(4H,m), 7.30(2H,m), 7.44(4H,s)

• (E)-4-[4-(3-Pyridyl)phenyl]-3-butenic acid



5

• m.p. (°C) : 205.5 to 206.0

10

• elemental analysis: as $C_{15}H_{13}NO_2$

15

	C	H	N
calculated (%)	75.30	5.48	5.85
found (%)	75.42	5.64	5.80

20

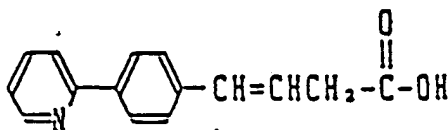
• NMR(DMSO- d_6) δ :

3.20(2H,d,J = 5.4Hz), 6.40(1H,dt,J = 15.5Hz,5.4Hz), 6.50(1H,d,J = 15.5Hz), 7.4(1H,m), 7.50(2H,d,J = 8.3Hz), 7.66(2H,d,J = 8.3Hz), 8.13(1H,d,J = 7.2Hz), 8.5(1H,bs), 8.8(1H,bs)

25

◦ (E)-4-[4-(2-Pyridyl)phenyl]-3-butenoic acid

30



35

• m.p. (°C) : 155.0 to 156.0

40

• elemental analysis: as $C_{15}H_{13}NO_2$			
	C	H	N
calculated (%)	75.30	5.48	5.85
found (%)	74.95	5.44	5.72

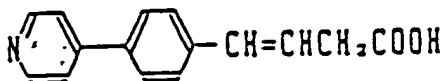
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• NMR(DMSO- d_6) δ :

3.25(2H,d,J = 5.7Hz), 6.45(1H,dt,J = 15.8Hz, 5.7Hz), 6.58(1H,d,J = 15.8Hz), 7.30-7.50(1H,m), 7.58-7.80(2H,d,J = 8.4Hz), 7.80-8.00(2H,m), 8.08(2H,d,J = 8.4Hz), 8.65(1H,m)

◦ (E)-4-[4-(4-Pyridyl)phenyl]-3-butenoic acid

50



55

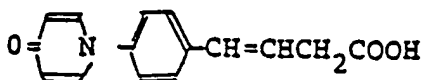
• m.p. (°C) : 209.5 to 211.0

* elemental analysis: as C ₁₅ H ₁₃ NO ₂			
	C	H	N
calculated (%)	75.30	5.48	5.85
found (%)	75.23	5.59	5.78

* H-NMR(DMSO-d₆) δ ;

3.25(2H,d,J = 6.1Hz), 6.48(1H,dt,J = 15.5Hz,6.1Hz), 6.60(1H,d,J = 15.5Hz), 7.4-8.0(6H,m), 8.7(2H,m)

◦ (E)-4-(1H-Pyridon-1-yl)phenyl]-3-butenic acid



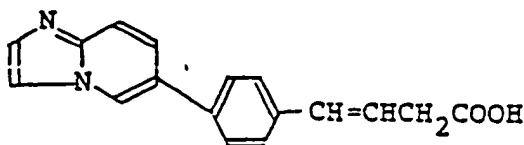
* m.p. (°C) : 275 (dec.)

* elemental analysis: as C ₁₅ H ₁₃ NO ₃			
	C	H	N
calculated (%)	70.58	5.13	5.49
found (%)	70.55	5.25	5.46

* H-NMR(DMSO-d₆) δ ;

3.21(2H,d,J = 5.6Hz), 6.1-6.3(2H,m), 8.36(1H,dt,J = 5.6Hz,16.3Hz), 6.60(1H,d,J = 16.3Hz), 7.3-7.7(4H,m), 7.8-8.1(2H,m)

◦ (E)-4-[4-(Imidazo[1,2-a]pyridin-6-yl)phenyl]-3-butenic acid



* m.p. (°C) : 254 to 260.0 (dec.)

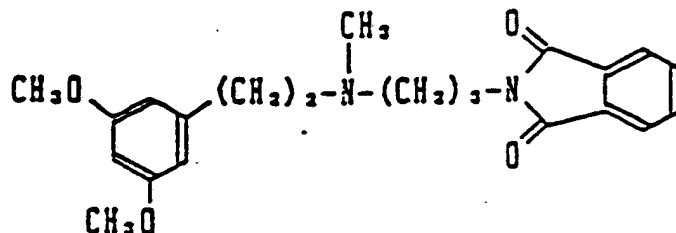
* elemental analysis: as C ₁₆ H ₁₄ N ₂ O ₂			
	C	H	N
calculated (%)	73.37	5.07	10.07
found (%)	73.15	5.16	10.00

* H-NMR(DMSO-d₆) δ ;

3.23(2H,d,J = 5.8Hz), 6.47(1H,dt,J = 15.5Hz,5.8Hz), 6.57(1H,d,J = 15.5Hz), 7.4-7.8(7H,m), 7.99(1H,s), 8.98(1H,s)

Preparative Example 5

N-[3-{N'-Methyl-N'-(2-(3,5-dimethoxyphenyl)ethyl)-amino}propyl]phthalimide



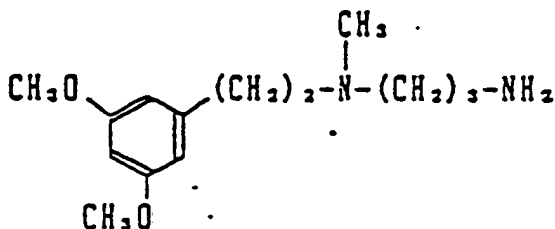
A mixture comprising 9.30 g of N-methyl-(2-(3,5-dimethoxyphenyl) ethyl)amine, 13.4 g of N-(3-bromopropyl)phthalimide, 7.2 g of potassium carbonate and 100 ml of dimethylformamide was stirred at 80° C for 8 hours. After the completion of the reaction, the reaction mixture was filtered to remove an inorganic matter. The filtrate was distilled to remove the dimethylformamide. Ethyl acetate was added to the residue. The obtained mixture was washed with water and extracted with dilute hydrochloric acid thrice. The extracts were combined, neutralized with concentrated aqueous ammonia and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The residue was purified by silica gel column chromatography (solvent: chloroform/methanol) to obtain 12.4 g of the title compound as a pale yellow oil (yield: 64%).

• NMR(CDCl₃) δ ;

1.6 -2.0(2H,m), 2.26(3H,s), 2.3-2.76(H,m), 3.5 -3.8(2H,m), 3.75(6H,s), 6.20-6.36(3H,m), 7.50-7.90(4H,m)

Preparative Example 6

N-Methyl-N-(2-(3,5-dimethoxyphenyl)ethyl)-1,3-propanediamine



9.24 g of the N-(3-(N'-methyl-N'-(2-(3,5-dimethoxyphenyl)ethyl)amino)propyl) phthalimide prepared in Preparative Example 5 and 4 ml of hydrazine monohydrate were dissolved in 100 ml of ethanol to obtain a solution. This solution was heated under reflux for 2 hours, cooled to a room temperature and filtered to remove generated precipitates. The filtrate was distilled to remove the ethanol. Chloroform was added to the residue. The obtained mixture was washed with an aqueous solution of caustic soda twice and with a saturated aqueous solution of common salt once, dried over anhydrous magnesium sulfate and distilled to remove the solvent. 5.81 g of the title compound was obtained as a pale yellow oil (yield: 96%). This oil was used in the following reaction without any additional purification.

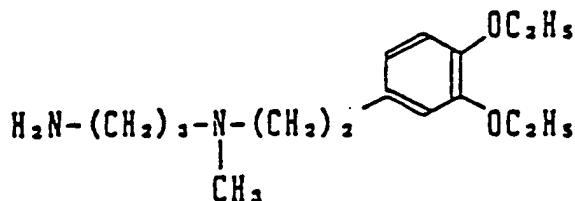
• NMR(CDCl₃) δ ;

1.4 -1.8(2H,m), 1.22(2H,bs), 2.28(3H,s), 2.3 -2.8(8H,m), 3.75(6H,s), 6.2-6.4(3H,m)

In a similar manner to the one described above, the following compounds were prepared:

o N-Methyl-N-[2-(3,4-diethoxyphenyl)ethyl]-1,3-propanediamine

5



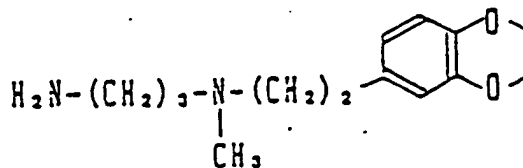
10

- yellow oil.
- NMR(CDCI₃) δ ;
1.21(2H,s), 1.3 -1.8(8H,m), 2.28(3H,s), 2.3 -2.9(8H,m), 4.04(2H,q,J = 7.0Hz), 4.07(2H,q,J = 7.0Hz), 6.6-7.0-(3H,m)

15

• N-Methyl-N-[2-(3,4-ethylenedioxyphenyl)ethyl]-1,3-propanediamine

20



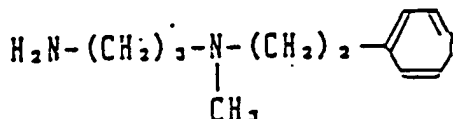
25

- yellow oil
- NMR(CDCI₃) δ ;
1.4 -2.1(4H,m), 2.27(3H,s), 2.3-2.9(8H,m), 4.22(4H,s), 6.4-6.8(3H,m)

30

• N-Methyl-N-[2-(4-pyridyl)ethyl]-1,3-propanediamine

35



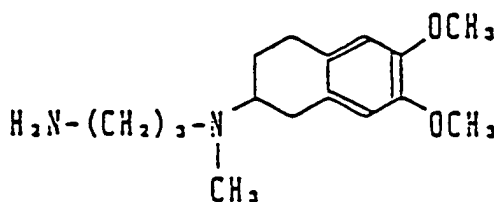
40

- yellow oil
- NMR(CDCI₃) δ ;
1.4 -1.8(2H,m), 2.0-2.9(13H,m), 6.9 -7.2(2H,m), 8.3-8.6(2H,m)

45

• N-Methyl-N-(6,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-1,3-propanediamine

50

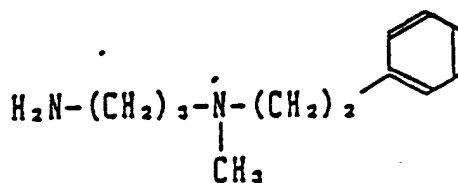


55

- yellow oil
- NMR(CDCI₃) δ ;
1.4 -2.2(6H,m), 2.32(3H,s), 2.4-2.9(9H,m), 3.83(6H,s), 6.56(2H,s)

o N-Methyl-N-(2-phenylethyl)-1,3-propanediamine

5



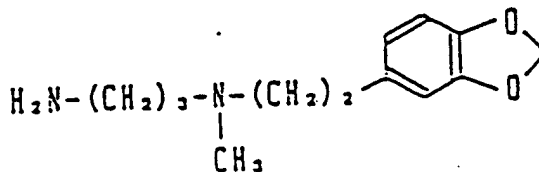
10

- yellow oil
- NMR(CDCl₃) δ ;
1.5–1.8(4H,m), 2.24(3H,s), 2.3–2.9(8H,m), 6.9–7.3(5H,m)

15

o N-Methyl-N-[2-(3,4-methylenedioxyphenyl)ethyl]-1,3-propanediamine

20



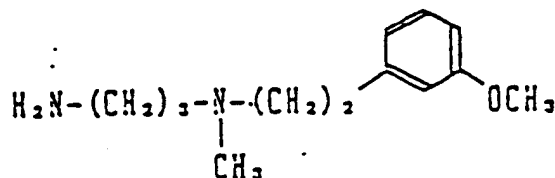
25

- yellow oil
- NMR(CDCl₃) δ ;
1.4–1.8(4H,m), 2.14(3H,s), 2.1–2.8(8H,m), 5.90(2H,s), 6.4–6.7(3H,m)

30

o N-Methyl-N-[2-(3-methoxyphenyl)ethyl]-1,3-propanediamine

35



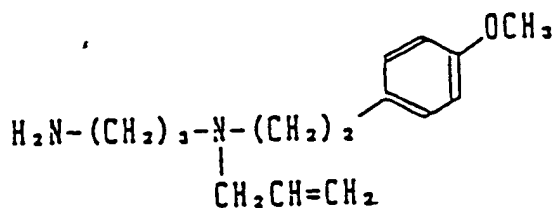
40

- yellow oil
- NMR(CDCl₃) δ ;
1.30(2H,s), 1.4–1.8(2H,m), 2.14(3H,s), 2.2–2.9(8H,m), 3.84(3H,s), 6.5–6.8(3H,m), 6.9–7.2(1H,m)

45

o N-Allyl-N-[2-(4-methoxyphenyl)ethyl]-1,3-propanediamine

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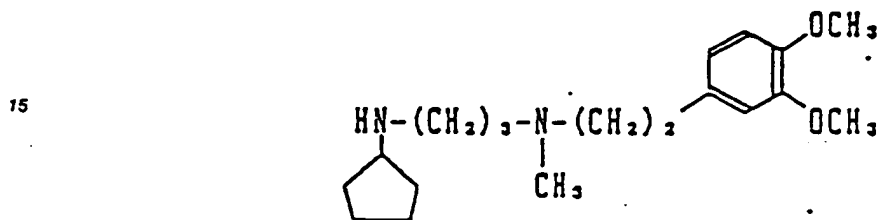
55

- yellow oil
- NMR(CDCl₃) δ ;
1.40(2H,s), 1.4 -1.8(2H,m), 2.4-2.88H,m), 3.10(2H,d,J = 7Hz), 3.74(3H,s), 4.96-5.30(2H,m), 5.76-6.02(1H,m), 6.6(2H,d,J = 10Hz), 7.0(2H,d,J = 10Hz)

5

Preparative Example 8N-Cyclopentyl-N'-methyl-N-[2-(3,4-dimethoxyphenyl)-ethyl]-1,3-propanediamine

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500 mg of N-methyl-N-[2-(3,4-dimethoxyphenyl)-ethyl]-1,3-propanediamine and 0.21 ml of cyclopentanone were dissolved in 5 ml of ethanol, followed by the addition of 10 mg of platinum oxide to carry out hydrogenation at a room temperature under 1 atm for 6 hours. The reaction mixture was filtered to remove the catalyst. The filtrate was concentrated under a reduced pressure to obtain 660 mg of the title compound as a yellow oil (yield: 100%).

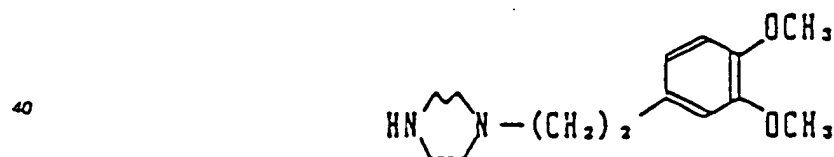
25

- NMR(CDCl₃) δ ;
1.1 -2.1(10H,m), 2.2 -2.9(12H,m), 2.9 -3.2(1H,m), 3.84(3H,s), 3.86(3H,s), 6.6 -6.9(3H,m)

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Preparative Example 9N-[2-(3,4-Dimethoxyphenyl)ethyl]homopiperazine

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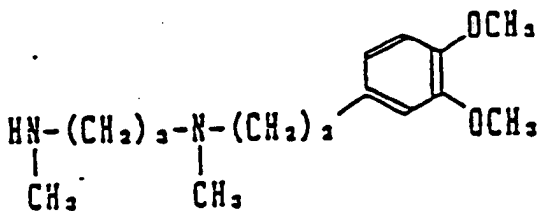
32.27g of homopiperazine, 13.2g of 2-(3,4-dimethoxyphenyl)ethyl chloride and 71.3 g of potassium carbonate were added to 500 ml of acetonitrile. The obtained mixture was heated under reflux for 20 hours, cooled and filtered. The filtrate was concentrated under a reduced pressure to obtain a residue. This residue was extracted with ether thrice. The extracts were combined, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent: chloroform/methanol/isopropylamine (100:10:1)) to obtain 13.40 g of the title compound as a yellow oil (yield: 77%).

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- NMR(CDCl₃) δ ;
1.83-1.98(2H,m), 2.39-3.11(13H,m), 3.83(3H,s), 3.84(3H,s), 6.55-6.83(3H,m)

55

Preparative Example 10N,N'-Dimethyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-1,3-propanediamine



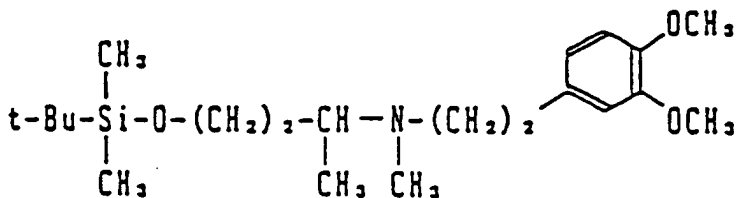
3.0 g of N-methyl-N-2-(3,4-dimethoxyphenyl)-ethyl-1,3-propanediamine was dissolved in a mixture comprising 1.8 ml of triethylamine and 100 ml of dichloromethane, followed by stirring under cooling with ice-water. 1.0 ml of methyl chloroformate was dropwise added to the obtained solution. The obtained mixture was stirred for several minutes and distilled to remove the dichloromethane. The residue was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and distilled to remove the solvent. Thus, 2.84 g of methylcarbamate was obtained. This methylcarbamate was dissolved in 100 ml of tetrahydrofuran to obtain a solution. This solution was dropwise added to a solution of 0.54 g of lithium aluminum hydride in 100 ml of tetrahydrofuran. The obtained mixture was heated under reflux for 2 hours and cooled with ice. 0.5 ml of water, 0.5 ml of a 15% aqueous solution of caustic soda and 1.5 ml of water were added to the resulting mixture successively. The obtained mixture was stirred at a room temperature for 30 minutes, followed by the addition of magnesium sulfate. The obtained mixture was filtered and the filtrate was distilled to remove the solvent. Thus, 2.30 g of the title compound was obtained as a light brown oil (yield: 72%).

* NMR(CDCl₃) δ :

1.44(1H,bs), 1.5-1.9(2H,m), 2.28(3H,s), 2.39(3H,s), 2.4-2.9(8H,m), 3.83(3H,s), 3.85(3H,s), 6.6-6.9(3H,m)

Preparative Example 11

N-Methyl-N-(4-(tert-butyldimethylsiloxy)-butan-2-yl)-[2-(3,4-dimethoxyphenyl)ethyl]amine

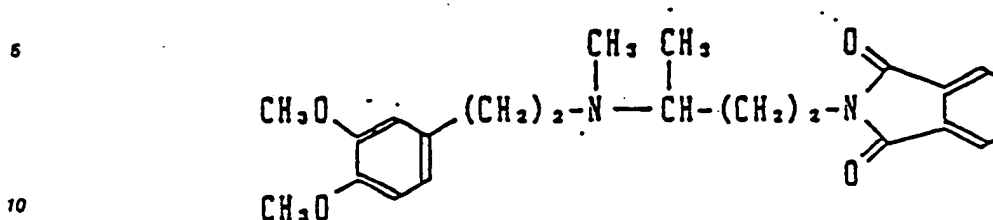


2.39 g of methanesulfonyl chloride was gradually added to 50 ml of a solution of 3.55 g of 4-(tert-butyldimethylsiloxy)butan-2-ol and 2.1 g of triethylamine in ether under cooling with ice. After 30 minutes, water was added to the obtained mixture. The obtained mixture was extracted with ether. The extract was dried over anhydrous sodium sulfate, filtered and distilled to remove the ether. The residue was dissolved in 50 ml of acetonitrile, followed by the addition of 6.74 g of N-methyl-[2-(3,4-dimethoxyphenyl)ethyl]amine hydroiodide and 7.7 g of potassium carbonate. The obtained mixture was heated under reflux for 12 hours, cooled and filtered to remove generated crystalline precipitates. The filtrate was concentrated under a reduced pressure and extracted with ether thrice. The ether layers were combined, washed with an aqueous solution of common salt, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under a reduced pressure and purified by silica gel column chromatography (solvent: chloroform/methanol (100:1)) to obtain 2.34 g of the title compound as a yellow oil (yield: 35%).

* NMR(CDCl₃) δ :

0.05(6H,s), 0.88(9H,s), 0.94(3H,d,J=6.1Hz), 1.26-1.95(2H,m), 2.24(3H,s), 2.36-3.03(5H,m), 3.58-3.81(2H,t,J=5.8Hz), 3.81(3H,s), 3.83(3H,s), 6.55-6.80(3H,m).

Preparative Example 12

N-[3-((N'-Methyl-N'-2-(3,4-dimethoxyphenyl)ethyl)-amino)butyl]phthalimide

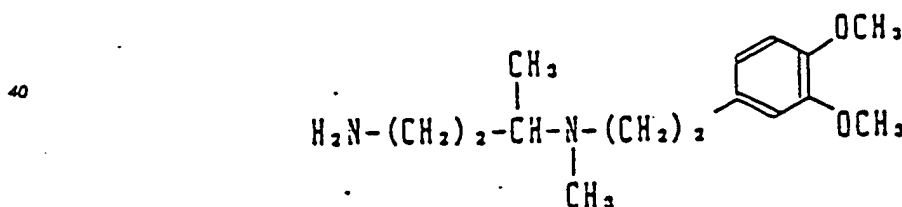
15 N-Methyl-N-(4-(t-butyl dimethylsiloxy)-butan-2-yl)-[2-(3,4-dimethoxyphenyl)ethyl]amine was dissolved in 12 ml of tetrahydrofuran to obtain a solution. 12 ml of a solution (1 mmol/ml) of tetra-n-butyl-ammonium fluoride in tetrahydrofuran was gradually added dropwise to the above solution at a room temperature. The obtained mixture was stirred at a room temperature for 3 hours and distilled to remove the solvent. The residue was extracted with ether thrice. The extracts were combined, dried over anhydrous sodium sulfate and concentrated under a reduced pressure. The residue was dissolved in 12 ml of tetrahydrofuran, followed by the addition of 900 mg of phthalimide and 1.61 of triphenylphosphine. 1.07 g of diethyl azodicarboxylate was gradually added to the obtained mixture at a room temperature. The obtained mixture was stirred overnight and distilled to remove the solvent. The residue was made acidic with 0.5 N hydrochloric acid and washed with ether. The aqueous layer was made basic with lithium hydroxide and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under a reduced pressure and purified by silica gel column chromatography (solvent: chloroform/methanol (100:1) to obtain 2.19 g of the title compound as a yellow oil (yield: 90%).

25 • NMR(CDCl₃) δ ;

0.96(3H,d,J=6.5Hz), 1.43-2.01(2H,m), 2.27(3H,s), 2.44-2.93(5H,m), 3.60-3.81(2H,m), 3.91(3H,s), 3.85-3.97(3H,s), 6.80(3H,m), 7.57-7.97(4H,m)

30 Preparative Example 13

35 3-[N-Methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)amino]butylamine



46.36 g of N-[3-(N'-methyl-2-(3,4-dimethoxyphenyl)ethyl)amino-3-methylpropyl]phthalimide and 7.03 g of hydrazine monohydrate were added to 500 ml of ethanol. The obtained mixture was heated under reflux for 2 hours, cooled and filtered to remove generated white precipitates. The filtrate was concentrated under a reduced pressure to obtain a residue. 200 ml of a 10% aqueous solution of sodium hydroxide was added to the residue, followed by the extraction with chloroform thrice. The extracts were combined, washed with a saturated aqueous solution of common salt, dried over anhydrous sodium sulfate and concentrated under a reduced pressure to obtain 26.88 g of the title compound as a yellow oil (yield: 86%).

50 • NMR(CDCl₃) δ ;

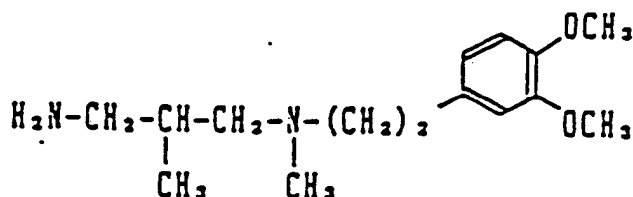
65 0.93(3H,d,J=6.3Hz), 0.93-1.82(4H,m), 2.12(3H,s), 2.24-2.93(7H,m), 3.78(3H,s), 3.83(3H,s), 6.54-6.84(3H,m)

Preparative Example 14

N-Methyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-methyl-1,3-propanediamine

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A mixture comprising 6.5 g of N-methyl-2-(3,4-dimethoxyphenyl)ethylamine hydroiodide, 1.8 g of methacrylonitrile and 2.4 g of triethylamine was heated at about 70 °C for 2.5 hours and cooled, followed by the addition of dichloromethane. The obtained mixture was washed with water, dried over magnesium sulfate and distilled to remove the solvent. The residue was purified by silica gel column chromatography (solvent: dichloromethane/ethanol (100:1)) to obtain 2.1 g of 3-[N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-amino]-2-methylpropanonitrile.

• NMR(CDCl₃) δ ;

1.24(3H,d,J=7Hz), 2.30(3H,s), 2.3-2.8 (7H,m), 3.8(6H,s), 6.5-6.8(3H,m)

2.1 g of the above nitrile and 0.2 ml of concentrated hydrochloric acid were dissolved in 30 ml of ethanol, followed by the addition of 0.2 g of platinum oxide to carry out hydrogenation under a hydrogen pressure of 2.1 kg/cm². The reaction mixture was filtered to remove the catalyst. The filtrate was distilled under a reduced pressure to remove the ethanol. The residue was made alkaline with a dilute solution of caustic soda. The aqueous layer was extracted with dichloromethane. The extract was washed with water, dried over magnesium sulfate and distilled under a reduced pressure to obtain 1.98 g of the title compound as a pale yellow oil (yield: 38%).

• NMR(CDCl₃) δ ;

0.90(3H,d,J=7Hz), 1.36(2H,s), 1.50-1.80(1H,m), 2.10(3H,s), 2.1-2.8(8H,m), 3.80(3H,s), 3.84(3H,s), 6.6-6.8 (3H, m)

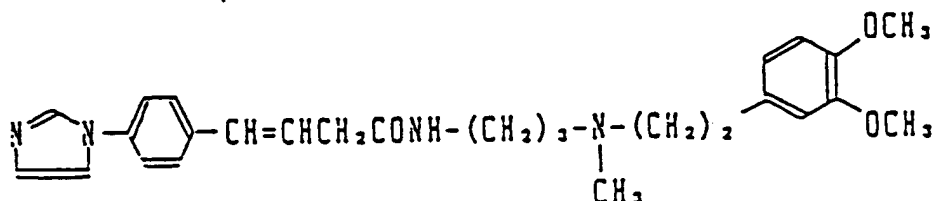
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Example 1

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(E)-N-[3-((N'-[2-(3,4-Dimethoxyphenyl)ethyl]-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

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62.1 g of (E)-4-[4-(1H-imidazol-1-yl)phenyl]-3-butenic acid and 36.8 g of N-hydroxybenzotriazole were added to 800 ml of acetonitrile containing 50% of water, followed by stirring under cooling with ice-water. 56.2 g of N,N'-dicyclohexylcarbodiimide was added to the obtained mixture in portions. The obtained mixture was stirred for 2 hours, followed by the dropwise addition of 65.4 g of N-methyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-1,3-propanediamine. After the completion of the above dropwise addition, the obtained mixture was stirred at a room temperature for 3 days and filtered to remove generated precipitates. The filtrate was sufficiently washed with ethyl acetate and extracted with dilute hydrochloric acid. The pH of the aqueous layer was adjusted with potassium carbonate to 9. The resulting layer was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, concentrated under a reduced pressure and purified by silica gel column chromatography (solvent:

chloroform/methanol/concentrated aqueous ammonia (1000:100:2)) to obtain 61.7 g of the title compound as a pale yellow oil (yield:52%).

* NMR(CDCl₃) δ ;

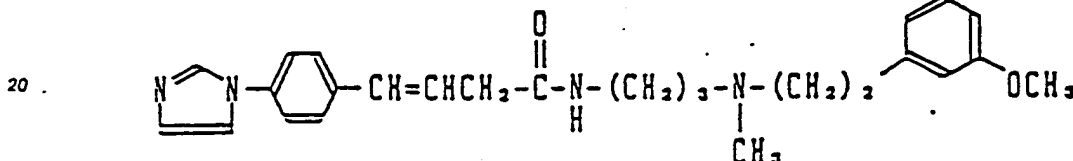
1.5 -1.8(2H,m), 2.20(3H,s), 2.3-2.8(6H,m), 3.02(2H,d,J=6.5Hz), 3.2 -3.5(2H, m), 3.84(3H,s), 3.86(3H,s),
6.20(1H,dt, J=6.1Hz,15.8Hz), 7.46(1H,d,J=15.8Hz), 8.5-8.8(3H,m), 7.1-7.5(7H,m), 7.77(1H,s)

Example 2

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(E)-N-[3-((N'-(2-(3,5-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

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60 g of (E)-4-[4-(1H-imidazol-1-yl)phenyl]-3-butenic acid was added to 1000 ml of acetonitrile containing 50% of water. The obtained mixture was stirred under cooling with ice-water, followed by the addition of 57.0 g of N,N'-dicyclohexylcarbodiimide and 37.3 g of N-hydroxybenzotriazole. The obtained mixture was stirred for about 4 hours to obtain a solution. A solution of 66.3 g of N-methyl-N-(2-(3,5-dimethoxyphenyl)-ethyl)-1,3-propanediamine in about 60 ml of acetonitrile was dropwise added to the above solution. The temperature of the obtained mixture was raised to a room temperature. The resulting mixture was stirred overnight, heated to a temperature of 30 to 40 °C and stirred for about 4 hours. After the completion of the reaction, the reaction mixture was filtered to remove generated precipitates. The filtrate was distilled to remove the acetonitrile, followed by the addition of ethyl acetate. The obtained mixture was extracted with dilute hydrochloric acid twice. The extracts were combined, neutralized with concentrated aqueous ammonia and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and distilled to remove the solvent, thus giving a yellow oil. This yellow oil was purified by silica gel column chromatography (solvent: chloroform/methanol/concentrated aqueous ammonia (100:10:0.2)) to obtain 74 g of the title compound as a pale yellow oil (yield: 62%).

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* NMR(CDCl₃) δ ;

1.5 -1.8(2H,m), 2.17 (3H,s), 2.3-2.5(6H,m), 3.01(2H,d,J=5.4Hz), 3.1 -3.5(2H,m), 3.72(6H,s), 6.0 -6.3(4H,m), 6.40(1H,d,J=15.5Hz), 7.1-7.5(7H,m), 7.78(1H,s)

Dihydrochloride dihydrate of the above produced butenamide was prepared in the following way.

45

258.9 g of the above produced product was dissolved in 7770 ml of acetone and 518 ml of water was added to the solution. The mixture was cooled with ice. 210 ml of an acetone solution of 100 ml of concentrated hydrochloric acid was added thereto dropwise and the mixture was stirred over one night. The precipitates obtained in the mixture was taken with filtration and washed with 1 liter of acetone. They were then dried at 55 degree C to obtain 270 g of the dihydrochloride dihydrate, being white to light yellow powder, with a production yield of 90.1 %. The product was found to show a heat-absorption peak around 100 degree C according to DSC. With reference to C27H34N4O3.2HCL.2H2O, results of its element analyses was:

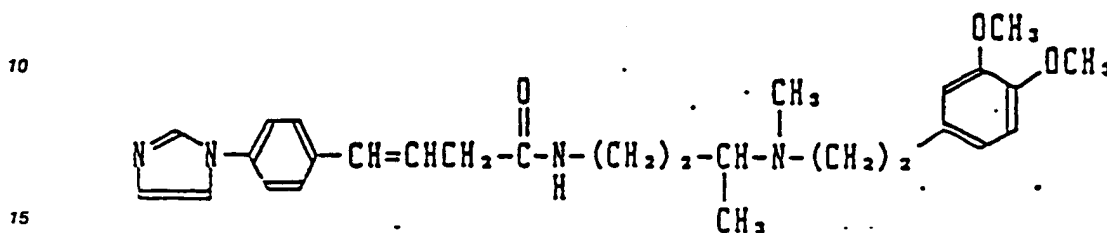
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	C	H	N
calcd.	56.74	7.05	9.80
found	56.72	6.93	9.86

Example 3

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)butyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-
butenamide



51.2 g of (E)-4-[4-(1H-imidazol-1-yl)phenyl]-3-butenic acid and 27.24 g of N-hydroxybenzotriazole were dissolved in a mixture comprising 500 ml of water and 500 ml of acetonitrile, followed by the addition of 41.6 g of N,N'-dicyclohexylcarbodiimide. The obtained mixture was stirred at 0 °C for 30 minutes, followed by the slow stepwise addition of a solution of the 3-(N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)amino)-butylamine prepared in Preparative Example 13 in 160 ml of acetonitrile. The obtained mixture was stirred at a room temperature overnight, heated at 40 °C for 2 hours, cooled and filtered. The filtrate was concentrated under a reduced pressure. The pH of the aqueous layer was adjusted to 3, followed by the addition of ethyl acetate. The obtained mixture was shaken to remove the organic layer. The remaining aqueous layer was made alkaline with sodium hydroxide and extracted with ethyl acetate thrice. The ethyl acetate layers were combined, dried over sodium sulfate and concentrated under a reduced pressure to obtain a residue. This residue was purified by silica gel column chromatography (solvent: chloroform/methanol/concentrated aqueous ammonia (1000:100:2)) to obtain 57.7 g of the title compound as a pale yellow oil (yield: 63%).

* NMR(400MHz, CDCl₃) δ ;

0.92(3H,d,J=6.2Hz), 1.40-1.65(2H,m), 2.18(3H,s), 2.50-2.70(4H,m), 2.75-2.90(1H,m), 3.02(2H,d,J=7.0Hz), 3.05-3.20(1H,m), 3.50-3.60(1H,m), 3.83(3H,s), 3.85(3H,s), 6.30(1H,dt,J=7.0Hz,16.1Hz), 6.47-(1H,d,J=16.1Hz), 6.62-6.71(2H,m), 6.76(1H,d,J=8.1Hz), 7.16(1H,bs), 7.26(1H,m), 7.29(2H,d,J=8.4Hz), 7.43-(2H,d,J=8.4Hz), 7.83(1H,bs)

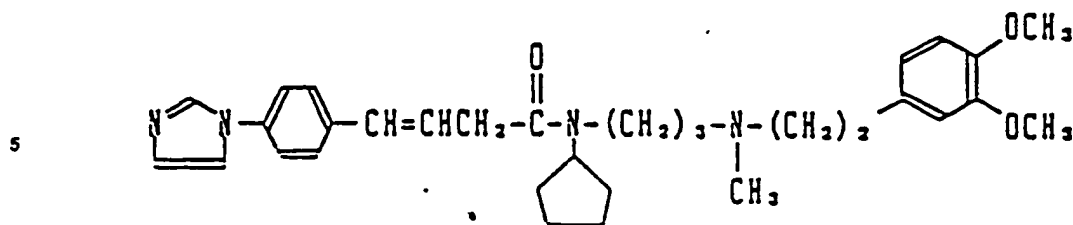
Examples 4 to 36

The compounds described in Examples 4 to 37 were each prepared in a similar manner to the one described in Example 1.

Namely, the compounds were each prepared by the same procedure as the one described in Example 1 except that the (E)-4-[4-(1H-imidazol-1-yl)phenyl]-3-butenic acid was replaced by the corresponding 4-substituted phenyl-3-butenic acid and the N-methyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-1,3-propanediamine was replaced by the corresponding substituted alkylendiamine.

Example 4

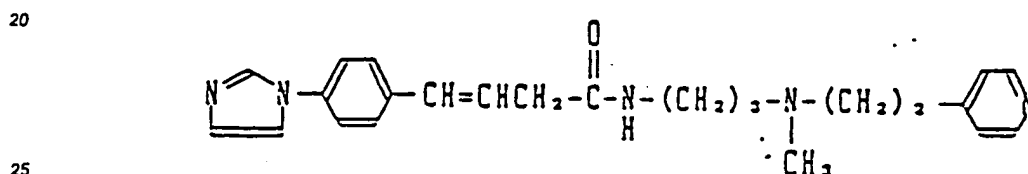
(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-N-cyclopentyl-4-(4-(1H-imidazol-1-yl)-
phenyl)-3-butenamide



10 • NMR(CDCl₃) δ ;
 1.2 -2.0(10H,s), 2.30(3H,s), 2.3 -2.8(6H,m), 3.0 -3.4(5H,m), 3.80(3H,s), 3.83(3H,s), 6.24-
 (1H,dt,J=7.2Hz,16.0Hz), 6.46(1H,d,J=16.0Hz), 6.5-6.8(3H,m), 7.1-7.5(6H,m), 7.77(1H,s)

15 Example 5

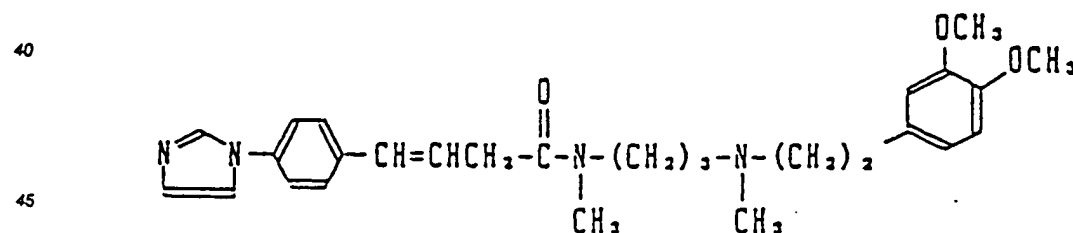
(E)-N-[3-((N'-(2-(4-Pyridylethyl)-N'-methyl)amino)propyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide]



30 • NMR(CDCl₃) δ ;
 1.5 -1.8(2H,m), 2.22(3H,s), 2.3-2.8(6H,m), 3.06(2H,d,J=5.7Hz), 3.1-3.5(2H,m), 6.26-
 (1H,dt,J=5.7Hz,15.8Hz), 6.51(1H,d,J=15.8Hz), 6.7-7.1(3H,m), 7.1 -7.5(6H,m), 7.78(1H,s), 8.3 -8.5(2H,m)

Example 6

35 (E)-N-Methyl-N-[3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)-
 phenyl)-3-butenamide



50 • NMR(400MHz, DMSO-d₅, 150 ° C) δ ;
 1.65-1.75(2H,m), 2.29(3H,s), 2.45(2H,m), 2.60-2.7(2H,m), 2.70 -2.80(2H,m), 2.94(3H,bs), 3.30-
 (2H,dd,J=6.6Hz,1.5Hz), 3.33-3.37(2H,m), 3.75(3H,s), 3.77(3H,s), 6.37(1H,dt,J=16.1Hz,6.6Hz), 6.52-
 (1H,dt,J=16.1Hz,1.5Hz), 6.74(1H,dd,J=8.1Hz,2.2Hz), 6.83(1H,d,J=2.2Hz), 6.84(1H,d,J=8.1Hz), 7.09(1H,bs),
 7.46 -7.55(4Hm.), 7.55-7.57(1H,m), 8.05(1H,bs)

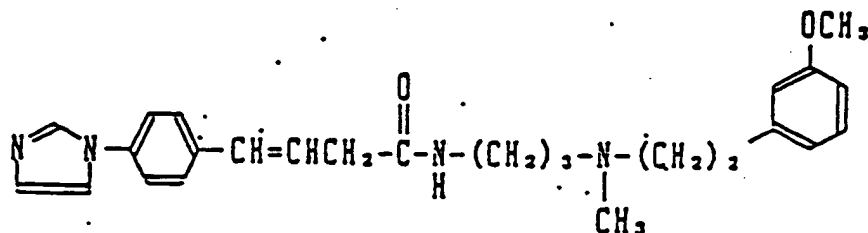
55 Example 7

(E)-N-[3-((N'-(2-(3-Methoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-

butenamide

5

10

• NMR(CDCl₃) δ ;

15 1.5 -1.8(2H,m), 2.20(3H,s), 2.40 -2.81(6H,m), 3.08(2H,d,J=6.8Hz), 3.2 -3.5(2H,m), 3.78(3H,s), 6.23-
(1H,dt,J=6.8Hz,16.2Hz), 6.48(1H,d,J=16.2Hz), 6.64-6.80(4H,m), 7.00-7.48(7H,m), 7.80(1H,br)

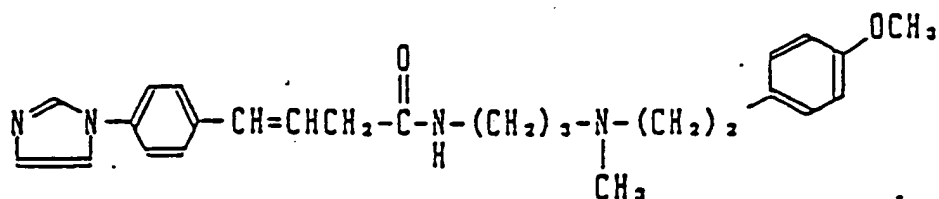
Example 8

20

(E)-N-[3-((N'-(2-(4-Methoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(1H-imidazol-1-yl)phenyl]-3-
butenamide

25

30

• NMR(CDCl₃) δ ;

35 1.44-1.80(2H,m), 2.20(3H,s), 2.30-2.80(6H,m), 3.0(2H,d,J=7.0Hz), 3.16 -3.40(2H,m), 3.70(3H,s), 6.20-
(1H,dt,J=7.0Hz,16.0Hz), 6.40(1H,d,J=16.0Hz), 6.60-7.5(11H,m), 7.72(1H,s)

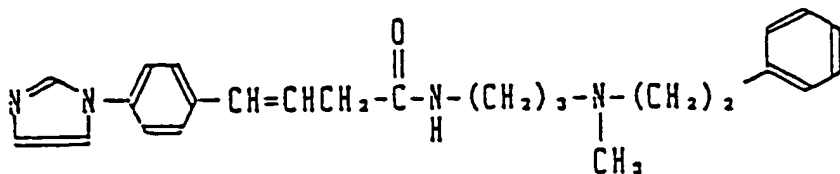
Example 9

40

(E)-N-[3-((N'-(2-Phenylethyl)-N'-methylamino)propyl)-4-(1H-imidazol-1-yl)phenyl]-3-butenamide

45

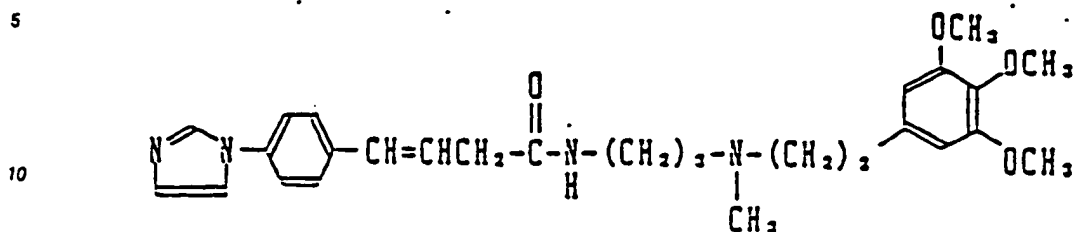
50

• NMR(CDCl₃) δ ;

55 1.5 -1.9(6H,m), 2.19(3H,s), 2.35 -2.90(5H,m), 3.00(2H,d,J=7.2Hz), 3.2 -3.5(2H,m), 6.20-
(1H,dt,J=7.2Hz,16.2Hz), 6.43(1H,d,J=16.2Hz), 6.75 -7.65(12H,m), 7.75(1H,br)

Example 10

(E)-N-[3-((N'-(2-(3,4,5-Trimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide



15

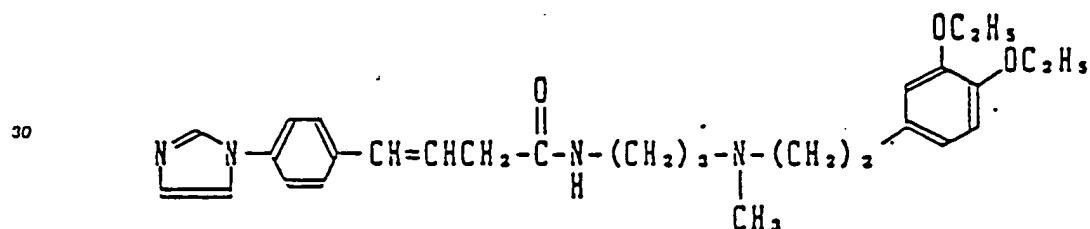
• NMR(CDCl₃) δ ;
 1.50–1.84(2H,m), 2.20(3H,s), 2.34–2.76(6H,m), 3.04(2H,d,J = 6.0Hz), 3.16–3.46(2H,m), 3.74(9H,s), 5.96–6.56-
 (4H,m), 7.04–7.48(7H,m), 7.72(1H,s)

Example 11

20

(E)-N-[3-((N'-(2-(3,4-Diethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

25



35

• NMR(CDCl₃) δ ;
 1.40(3H,t,J = 7.0Hz), 1.41(3H,t,J = 7.0Hz), 1.5 –1.8 (2H,m), 2.21(3H,s), 2.3 –2.8(6H,m), 3.04(2H,d,J = 5.7Hz),
 3.2 –3.5(2H,m), 3.99(2H,q,J = 7.0Hz), 4.00(2H,q,J = 7.0Hz), 6.18(1H,dt,J = 5.7Hz,15.5Hz), 6.44-
 (1H,d,J = 15.5Hz), 6.5–6.8(3H,m), 7.0 –7.5(7H,m), 7.75(1H,bs)

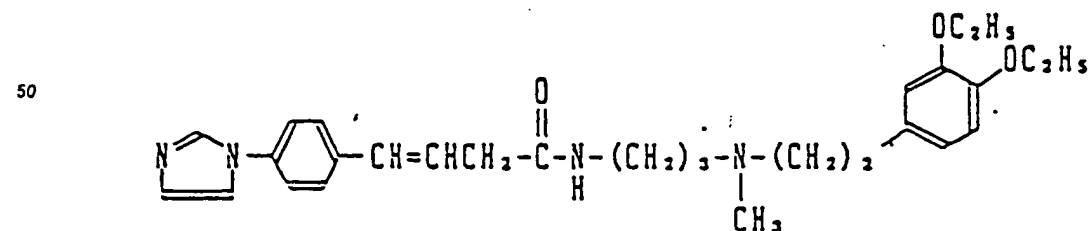
40

Example 12

45

(E)-N-[3-((N'-(2-(2,5-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

50



• NMR(CDCl₃) δ ;
 1.50–1.80(2H,m), 2.20(3H,s), 2.40– 2.80(6H,m), 3.04(2H,d,J = 5.7Hz), 3.16–3.44(2H,m), 3.64(3H,s), 3.68-

(3H,s), 5.90–6.52(2H,m), 6.52–6.80(3H,m), 7.04–7.60(7H,m), 7.72(1H,s)

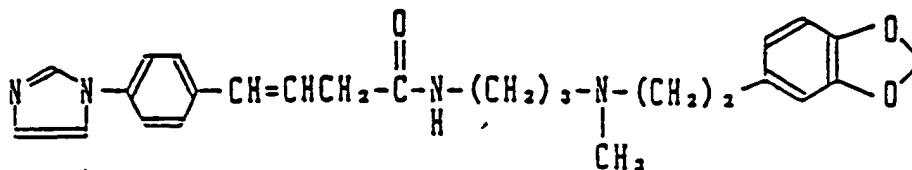
Example 13

5

(E)-N-[3-((N'-(2-(3,4-Methylenedioxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

10

15



• NMR(CDCl₃) δ ;

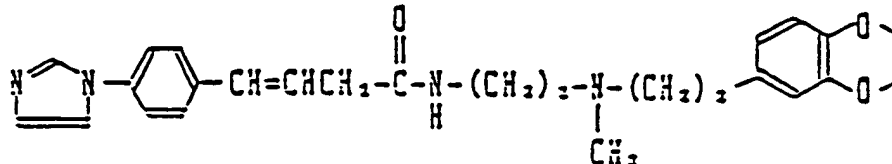
1.45–1.80(2H,m), 2.16(3H,s), 2.30–2.70(6H,m), 3.04(2H,d,J = 5.4Hz), 3.10–3.40(2H,m), 5.80(2H,s), 6.0–6.72-
20 (5H,m), 7.04–7.60(7H,m), 7.76(1H,s)

= Example 14

25 (E)-N-[3-((N'-(2-(3,4-Ethylenedioxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

30

35



• NMR(CDCl₃) δ ;

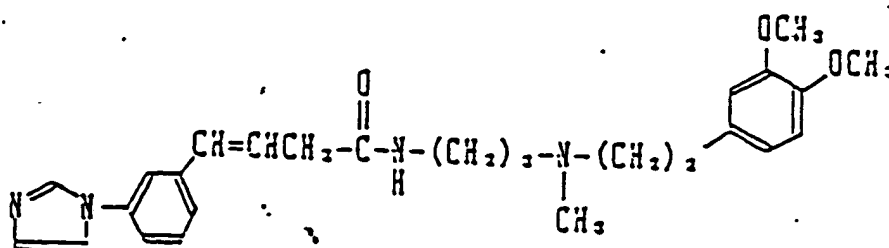
1.5–1.8(2H,m), 2.18(3H,s), 2.3–2.7(6H,m), 3.06(2H,d,J = 6.2Hz), 3.2–3.5(2H,m), 4.18(4H,s), 6.0–6.8(5H,m),
40 7.0–7.5(7H,m), 7.78(1H,s)

Example 15

45 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(3-(1H-imidazol-1-yl)phenyl)-3-butenamide

50

55



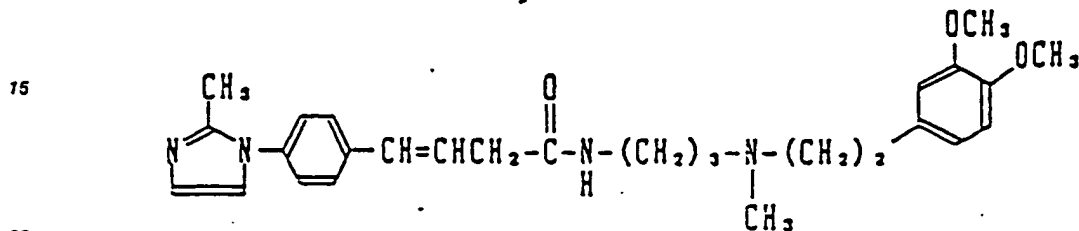
• NMR(CDCl₃) δ :

1.5 -1.8(2H,m), 2.21(3H,s), 2.3-2.8(6H,m), 3.00(2H,d,J=6.1Hz), 3.1-3.5(2H,m), 3.78(3H,s), 3.80(3H,s), 6.26-
(1H,dt,J=16.6Hz,6.1Hz), 6.38(1H,d,J=16.6Hz), 6.5-6.7(3H,m), 6.9-7.2(7H,m), 7.72(1H,bs)

6 Example 16

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(2-methyl-1H-imidazol-1-yl)-phenyl)-3-butenamide

10



• NMR(CDCl₃) δ :

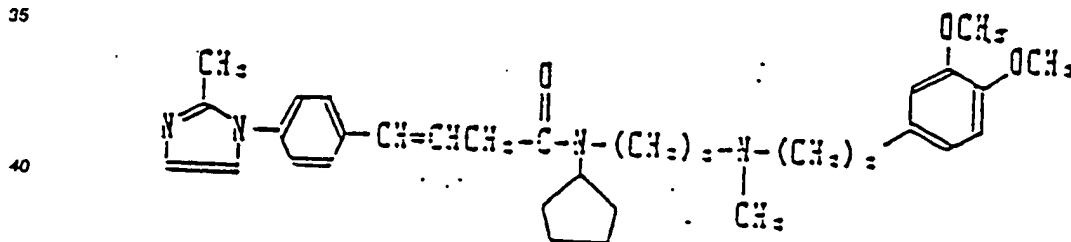
1.5 -1.9(2H,m), 2.23(3H,s), 2.33(3H,s), 2.3-2.8(6H,m), 3.06(2H,d,J=5.7Hz), 3.1-3.5(2H,m), 3.82(3H,s), 3.85-
25 (3H,s), 6.30(1H,dt,J=5.7Hz,15.4Hz), 6.53(1H,d,J=15.4Hz), 6.5-6.8(3H,m), 6.95(1H,d,J=1.3Hz), 7.00-
(1H,d,J=1.3Hz), 7.0-7.2(2H,m), 7.2-7.5(3H,m)

Example 17

30

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-N-cyclopentyl-4-(4-(2-methyl-1H-imidazol-1-yl)phenyl)-3-butenamide

35



45 • NMR(CDCl₃) δ :

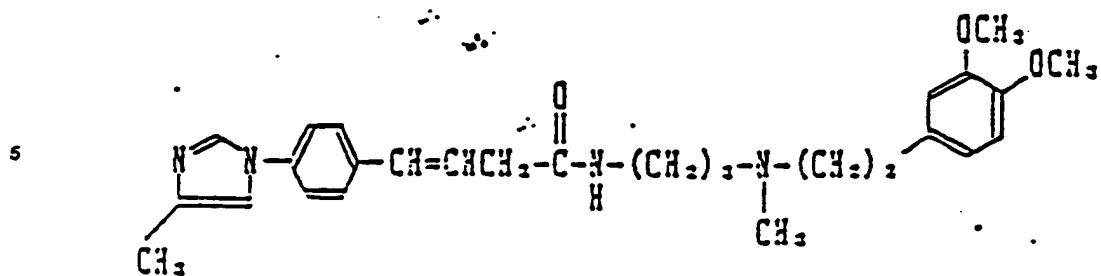
1.20-2.08(10H,m), 2.31(3H,s), 2.34(3H,s), 2.40-2.87(6H,m), 2.95-3.40(5H,m), 3.81(3H,s), 3.84(3H,s),
6.20-6.50(2H,m), 6.51-6.80(3H,m), 6.81-7.00(2H,m), 7.00-7.20(2H,m), 7.30-7.50(2H,m)

Example 18

50

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(4-methyl-1H-imidazol-1-yl)-phenyl)-3-butenamide

55

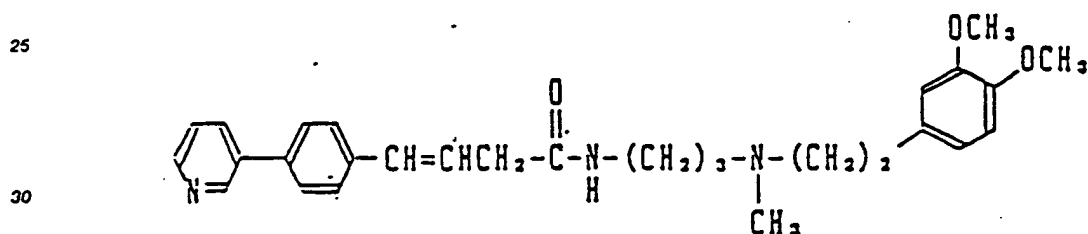


• NMR(CDCl₃) δ ;

1.5 -1.8(2H,m), 2.20(3H,s), 2.27(3H,s), 2.3 -2.8(6H,m), 3.04(2H,d, J=5.7Hz), 3.2 -3.5(2H,m), 3.82(3H,s),
 15 3.84(3H,s), 6.23(1H,dt,J=5.7Hz,15.8Hz), 6.49(1H,d,J=15.8Hz), 6.96(1H,d,J=0.9Hz), 7.1-7.5(5H,m), 7.67-
 (1H,d,J=0.9Hz)

Example 19

20 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(3-pyridyl)phenyl)-3-butenamide



• NMR(CDCl₃) δ ;

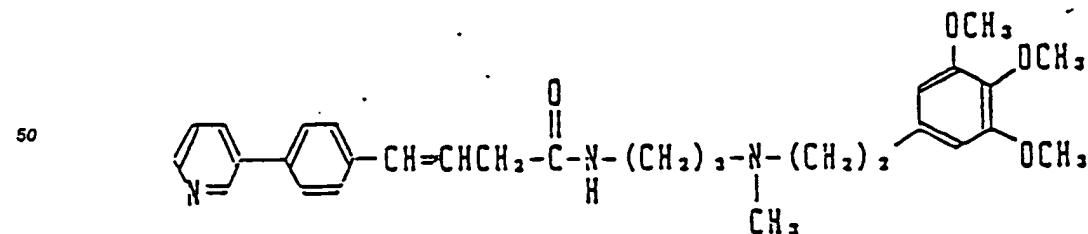
35 1.5 -1.7(2H,m), 2.18(3H,s), 2.3-2.8(6H,m), 3.04(2H,d,J=5.4Hz), 3.2 -3.5(2H,m), 3.78(3H,s), 3.80(3H,s), 6.30-
 (1H,dt,J=15.8Hz,5.4Hz), 6.44(1H,d,J=15.8Hz), 6.5-6.8(3H,m), 7.2-7.5(6H,m), 7.76(1H,dm,J=8.3Hz), 8.50-
 (1H,dd,J=5.4Hz,2.5Hz), 8.76(1H,d,J=2.5Hz)

Example 20

40

(E)-N-[3-((N'-(2-(3,4,5-Trimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(3-pyridyl)phenyl)-3-
butenamide

45



• NMR(CDCl₃) δ ;

1.5 -1.8(2H,m), 2.20(3H,s), 2.30 -2.70(6H,m), 3.08(2H,d,J=5.4Hz), 3.1 -3.5(2H,m), 3.78(9H,s), 6.30(2H,s),

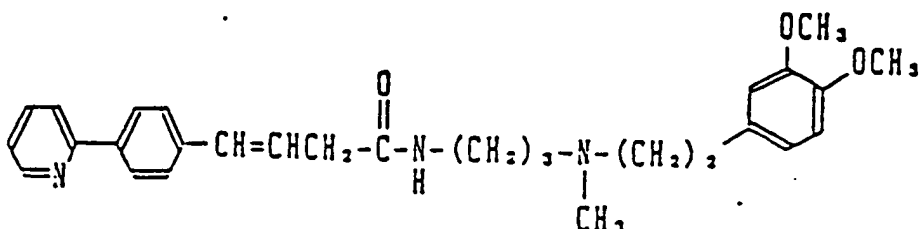
6.36(1H,dt,J=5.4Hz,15.8Hz), 6.46(1H,d,J=15.8Hz), 7.1-7.6(6H,m), 7.75(1H,d,J=7.2Hz), 8.5(1H,bs), 8.75(1H,bs)

Example 21

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(2-pyridyl)phenyl)-3-butenamide

10

15



20

• NMR(CDCl₃) δ :

1.5 -1.9(2H,m), 2.12(3H,s), 2.2-2.8(6H,m), 3.08(2H,d,J=6.5Hz), 3.2 -3.6(2H,m), 3.82(6H,s), 6.34(1H,dt,J=15.8Hz,6.5Hz), 6.50(1H,d,J=15.8Hz), 6.6 -6.8(3H,m), 7.1-7.4(2H,m), 7.46(2H,d,J=8.3Hz), 7.7 -7.8(2H,m), 7.96(2H,d,J=8.3Hz), 8.70(1H,m)

25

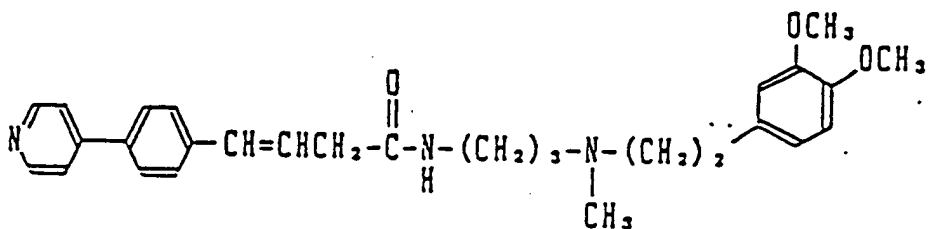
Example 22

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(4-pyridyl)phenyl)-3-butenamide

30

35

40

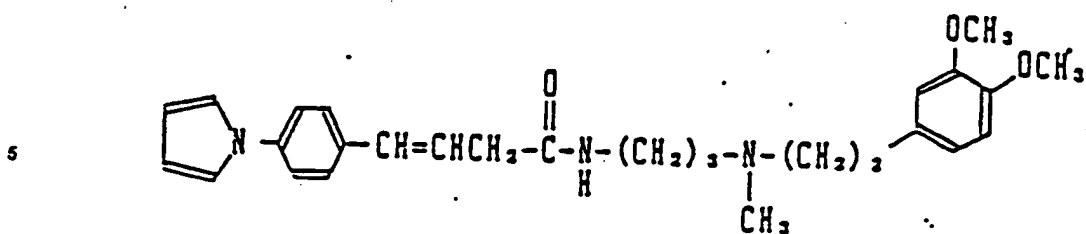


45

Example 23

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-pyrrol-1-yl)phenyl)-3-butenamide

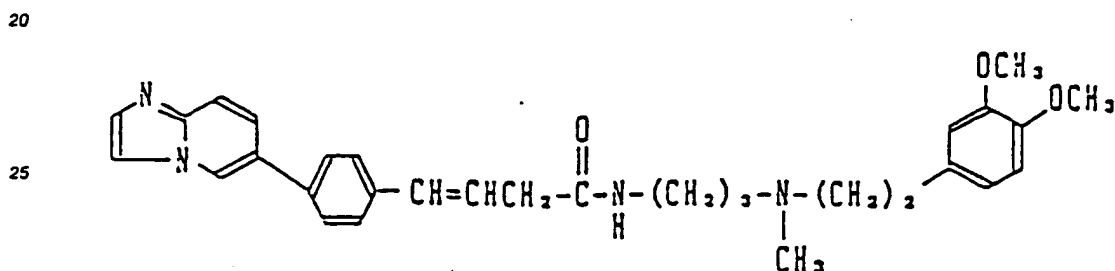
55



10 • NMR(CDCl₃) δ ;
 1.48–1.92(2H,m), 2.19(3H,s), 2.35–2.80(6H,m), 3.05(2H,d,J=6.2Hz), 3.20–3.60(2H,m), 3.82(6H,s), 6.0–6.5-
 (4H,m), 6.5–6.8(3H,m), 6.9–7.1(2H,m), 7.1–7.4(4H,m)

15 Example 24

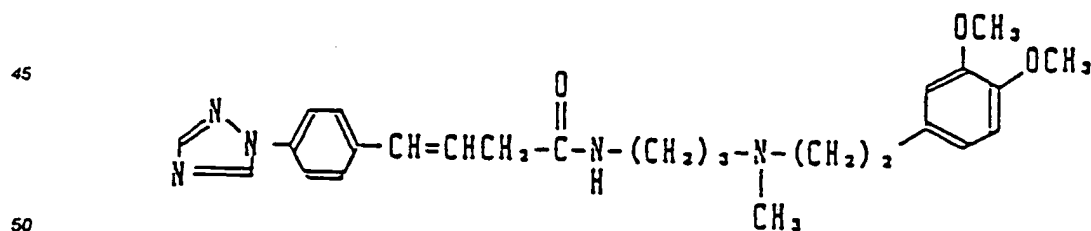
(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(imidazo[1,2-a]pyridin-6-yl)-
 phenyl)-3-butenamide



30 • NMR(CDCl₃) δ ;
 1.6–1.9(2H,m), 2.23(3H,s), 2.7–2.8(6H,m), 3.09(2H,d,J=6.1Hz), 3.3–3.5(2H,m), 3.82(3H,s), 3.85(3H,s), 6.36-
 (1H,dt,J=16.2Hz,6.1Hz), 6.52(1H,d,J=16.2Hz), 6.6–6.9(3H,m), 7.2–7.6(8H,m), 8.46(1H,m)

35 Example 25

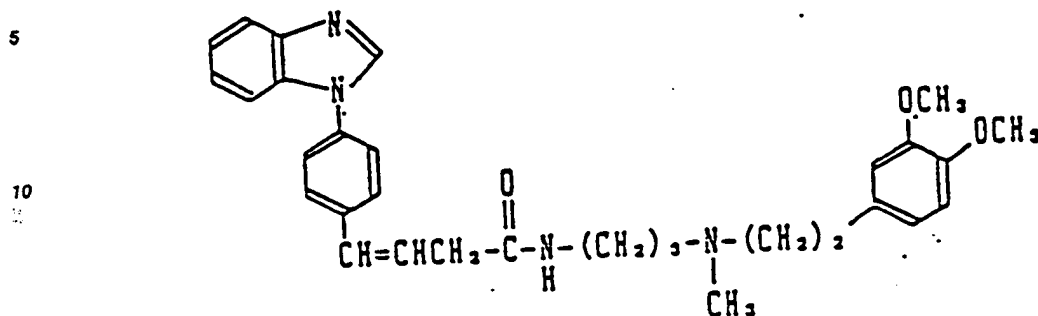
(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-
 40 butenamide



• NMR(CDCl₃) δ ;
 1.50–1.85(2H,m), 2.20(3H,s), 2.18–2.80(6H,m), 3.02(2H,d,J=6.0Hz), 3.2–3.5(2H,m), 3.80(3H,s), 3.82(3H,s),
 55 6.22(1H,dt,J=16.0Hz), 6.48(1H,d,J=16.2Hz), 6.35–6.78(3H,m), 7.0–7.3(1H,m), 7.3–7.6(4H,m), 8.00(1H,s),
 8.44(1H,s)

Example 26

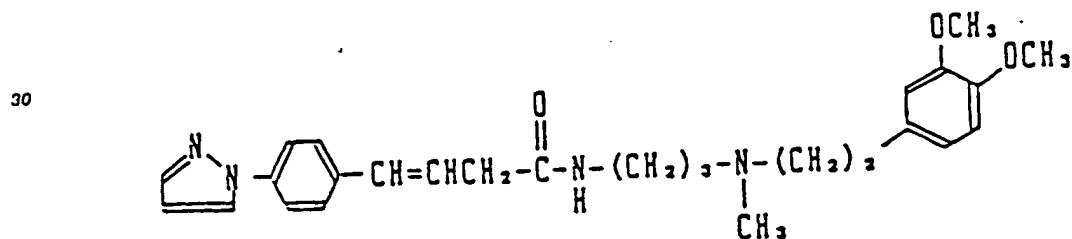
(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-benzimidazol-1-yl)phenyl)-3-butenamide



• NMR(CDCI₃) δ ;
 1.44-1.80(2H,m), 2.20(3H,s), 2.32-2.80(6H,m), 3.0(2H,d,J=6.0Hz), 3.10-3.44(2H,m), 3.72(3H,s), 3.76(3H,s),
 6.0-6.44(2H,m), 6.48-6.76(3H,m), 7.10-7.6(9H,m), 8.0(1H,s)

Example 27

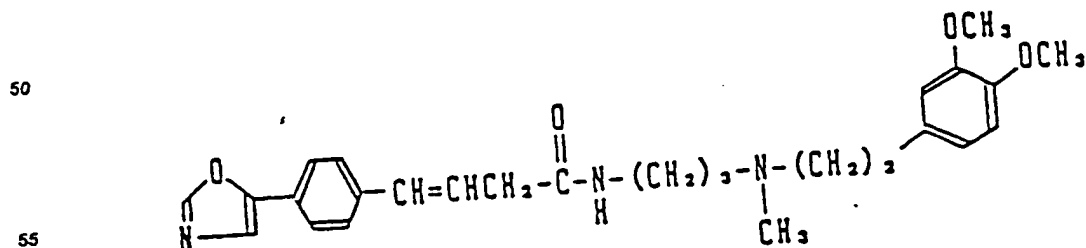
25 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1H-pyrazol-1-yl)phenyl)-3-butenamide



• NMR(CDCI₃) δ ;
 1.4-1.8(2H,m), 2.16(3H,s), 2.3-2.7(6H,m), 3.0(2H,d,J=5.0Hz), 3.16-3.40(2H,m), 3.76(6H,s), 5.96-6.76-
 (6H,m), 7.2-7.7(7H,m), 7.8(1H,d,J=3Hz)

Example 28

45 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl]-4-(4-(1,3-oxazol-5-yl)phenyl)-3-butenamide

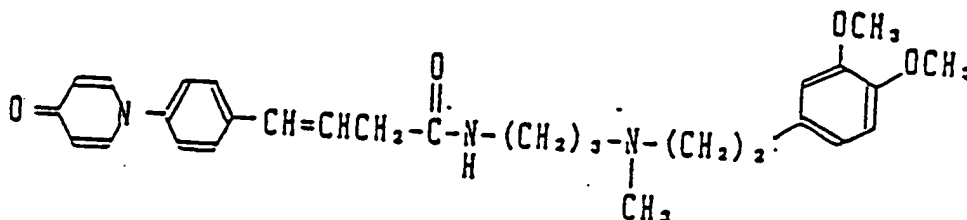


• NMR(CDCl₃) δ :

1.50-1.86(2H,m), 2.18(3H,s), 2.30-2.76(6H,m), 3.05(2H,d,J=6.2Hz), 3.20-3.54(2H,m), 3.82(3H,s), 3.84-
(3H,s), 6.22(1H,dt, J = 15.1Hz,8.2Hz), 6.44(1H,d,J = 15.1Hz), 6.56 -6.76(3H,m), 7.28(1H,s), 7.3 -7.66(5H,m),
7.86(1H,s)

Example 29

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-
butenamide methyl)amino)propyl]-4-(4-(1H-pyridon-1-yl)phenyl)-3-

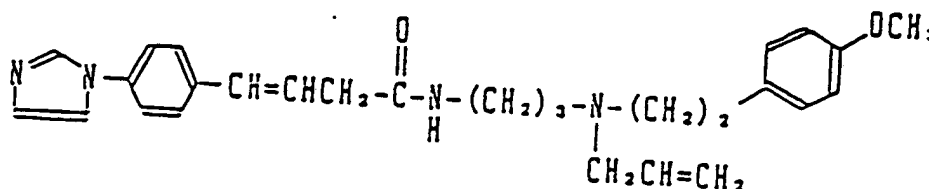


• NMR(CDCl₃) δ :

1.5 -1.8(2H,m), 2.23(3H,s), 2.3-2.8(6H,m), 3.05(2H,d,J=5.3Hz), 3.2 -3.5(2H,m), 3.82(3H,s), 3.84(3H,s), 6.0
-6.5(4H,m), 6.5-6.8(3H,m), 7.0-7.6(7H,m)

Example 30

(E)-N-[3-((N'-(2-(4-Methoxyphenyl)ethyl)-N'-allyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

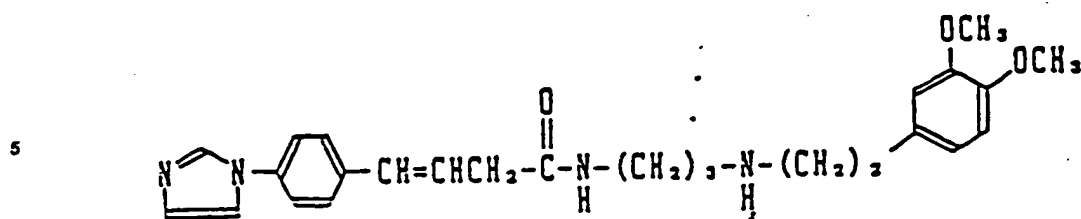


• NMR(CDCl₃) δ :

1.50-1.80(2H,m), 2.4 -2.7(6H,m), 3.04 (2H,d,J=5.0Hz), 3.03(2H,d,J=7.2Hz), 3.16-3.44(2H,m), 3.7(3H,s),
4.96 -5.24(2H,m), 5.5 -6.0(1H,m), 6.0-7.5(13H,m), 7.76(1H,s)

Example 31

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)amino)propyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

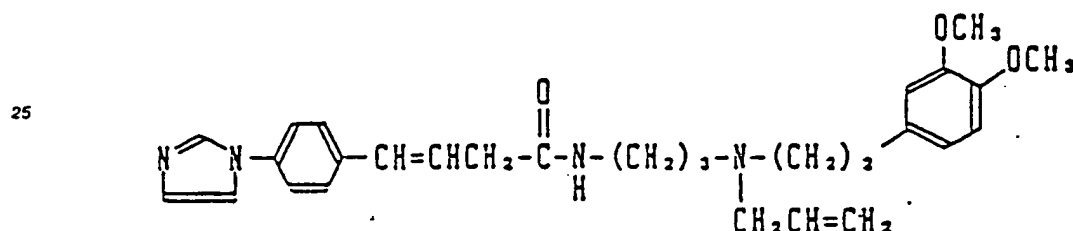


10 • NMR(CDCl₃) δ ;
 1.5 -1.9(2H,m), 2.32(1H,brs), 2.50 -3.00(6H,m), 3.08(2H,d,J=7.0Hz), 3.2 -3.5(2H,m), 3.84(3H,s), 3.86(3H,s),
 6.26(1H,dt,J=7.0Hz,14.4Hz), 6.50(1H,d,J=14.4Hz), 6.58 -6.80(3H,m), 7.0 -7.55(7H,m), 7.78(1H,s)

15 Example 32

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)N'-allyl)amino)propyl]-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

20

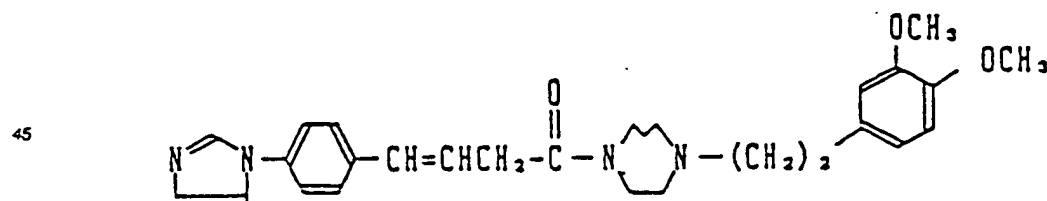


• NMR(CDCl₃) δ ;
 1.55-1.80(2H,m), 2.30-2.74(6H,m), 2.80-3.25(4H,m), 3.2 -3.5(2H,m), 3.74(6H,s), 4.98-5.18(2H,m), 6.24-
 (1H,dt,J=5.4Hz,16.2Hz), 6.47(1H,d,J=16.2Hz), 6.62-7.45(10H,m), 7.78(1H,s)

35 Example 33

N-[2-(3,4-Dimethoxyphenyl)ethyl]-N'-[(E)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenoyl]homopiperazine

40

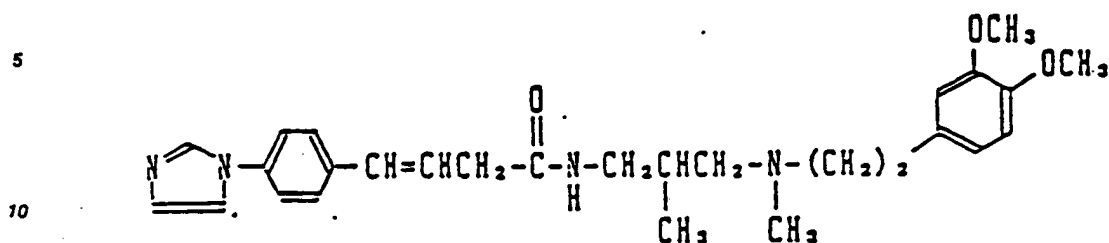


50

• NMR(CDCl₃) δ ;
 1.73-2.07(2H,m), 2.41-3.13(8H,m), 3.21-3.83(6H,m), 3.83(3H,s), 3.85(3H,s), 6.37-6.57(2H,m), 6.61-6.89-
 (3H,m), 7.14-7.65(6H,m), 7.83(1H,s)

55 Example 34

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino)-2-methylpropyl]-4-(4-(1H-imidazol-1-yl)-

phenyl)-3-butenamide

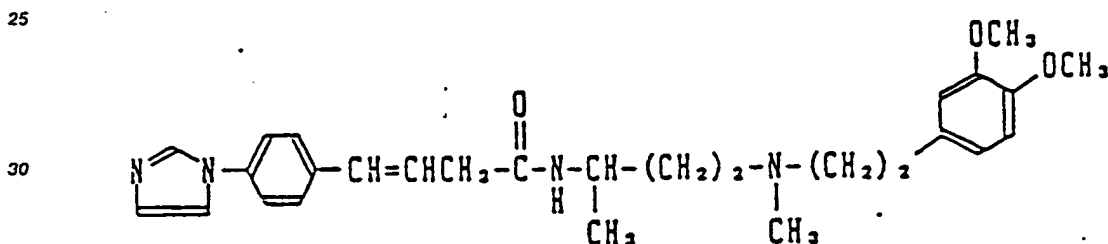
• NMR(CDCl₃) δ ;

15 0.84(3H,d,J=7.0Hz), 2.16(3H,s), 2.2 -2.8(7H,m), 3.0(2H,d,J=6.0Hz), 3.4 -3.8(2H,m), 3.8(6H,s), 5.96-6.8-(5H,m), 7.0 -7.5(6H,m), 7.76(1H,s), 7.8-8.1(1H,m)

Example 35

20

(E)-N-{4-[(N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methyl)amino]butan-2-yl]-4-(1H-imidazol-1-yl)phenyl}-3-butenamide



35 • NMR(CDCl₃) δ ;

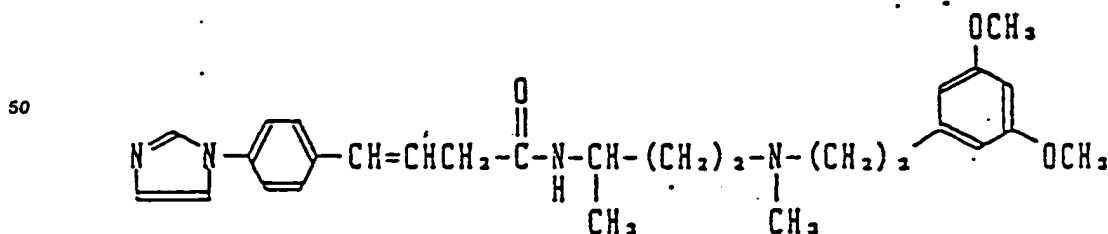
1.16(3H,d,J=7.0Hz), 1.4 -1.8(2H,m), 2.2(3H,s), 2.3-2.8(6H,m), 3.74(3H,s), 3.76(3H,s), 3.9 -4.2(1H,m), 6.0-6.8(5H,m), 7.04-7.6(7H,m), 7.74(1H,s)

Example 36

40

(E)-N-{4-[(N'-(2-(3,5-Dimethoxyphenyl)ethyl)-N'-methyl)amino]butan-2-yl]-4-(1H-imidazol-1-yl)phenyl}-3-butenamide

45



• NMR(CDCl₃) δ ;

1.18(3H,d,J=7.2Hz), 1.4 -2.0(2H,m), 2.21(3H,s), 2.3 -2.8(6H,m), 3.01(2H,d,J=6.6Hz), 3.73(6H,s), 3.9 -4.3-

(1H,m), 6.24(3H,s), 6.27(1H,dt,J=6.6Hz,15.8Hz), 6.44(1H,d,J=15.8Hz), 7.0-7.5(7H,m), 7.76(1H,s)

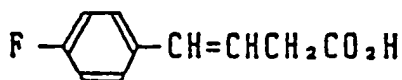
Examples of the compound II

5

Manufacturing Example 1

10

(E)-4-(4-fluorophenyl)-3-butenic acid



15

NMR (CDCl₃) ; δ

74.4 g of 4-fluorobenzaldehyde and 233.6 g of β-carboxyethyl-triphenyl phosphonium chloride were suspended in 700 ml of tetrahydrofuran and these were incubated on ice and stirred. Into this 500 ml tetrahydrofuran solution of 141.4 g of potassium tert-butoxide was added slowly dropwise. 30 minutes after temperature was brought to room temperature and then they were stirred for 10 hours. After adding thereto ice water and cleaning with ether, the hydrogen-ion concentration of water layer was set to pH2 with undiluted hydrochloric acid. Extraction was then made with ethyl acetate. After drying with magnesium sulfate and concentration made under reduced pressure, the solid obtained was recrystallized from hydrous ethanol, and 53.98 g of marked compound (yield: 50%) was obtained as white needle crystal. melting point (°C): 114 to 115

30

o Value of elemental analysis: as C ₁₀ H ₉ FO ₂			
	C	H	F
Theoretical value	66.64	5.04	10.55
Observed value	66.64	5.02	10.44

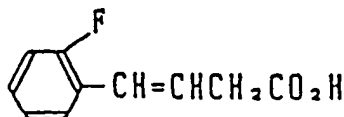
35

3.28 (2H,d,J=6.5 Hz), 6.16 (1H, dt,J=6.5Hz,16.2Hz), 6.50 (1H,d,J=16.2Hz), 7.2 to 7.5(4H,m), 9.36- (1H,br)

In a same way as above, the following compound was obtained.

40

(E)-4-(2-fluorophenyl)-3-butenic acid



45

o Fusing Point (°C): 61 to 62

50

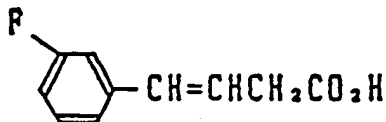
o Value of Elemental Analysis: as C ₁₀ H ₉ FO ₂		
	C	H
Theoretical Value:	66.64	5.04
Observed Value:	66.75	5.03

55

o NMR(CDCl₃) δ ;

3.30(2H,d,J = 6.5Hz), 6.17(1H,dt,J = 6.5Hz,16.6Hz), 6.68(1H,d,J = 16.6Hz), 6.9–7.4(4H,m), 11.62(1H,br)

(E)-4-(3-fluorophenyl)-3-butenic acid



o Fusing Point (°C): 66.5 to 67

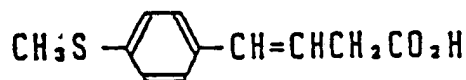
o Value of Elemental Analysis: as C₁₀H₉FO₂

	C	H	F
Theoretical Value:	66.64	5.04	10.55
Observed Value:	66.66	4.95	10.51

o NMR(CDCl₃) δ ;

3.28(2H,d,J = 6.5Hz), 6.24(1H,dt,J = 6.5Hz,16.2Hz), 6.50(1H,d,J = 16.2Hz), 7.7–8.4(4H,m), 11.92(1H,br)

(E)-4-(4-(methylthio)phenyl)-3-butenic acid



o Fusing Point(°C): 131 to 132

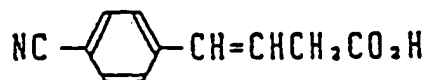
o Value of Elemental Analysis: as C₁₁H₁₂O₂S

	C	H	S	
Theoretical Value:	63.43	5.81	15.40	(%)
Observed Value:	63.78	5.78	15.34	(%)

o NMR(CDCl₃) δ ;

2.47(3H,s), 3.28(2H,d,J = 6Hz), 6.16(1H,dt,J = 7Hz,15Hz), 6.44(1H,d,J = 15Hz), 7.01–7.35(4H,m)

(E)-4-(4-cyanophenyl)-3-butenic acid



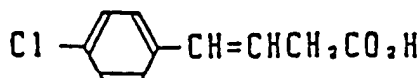
o Fusing Point (°C): 111 to 113

o Value of Elemental Analysis: as $C_{11}H_9NO_2$

	C	H	N
Theoretical Value (%):	70.58	4.85	7.48
Observed Value (%):	70.61	4.98	7.41

o NMR($CDCl_3$) δ :

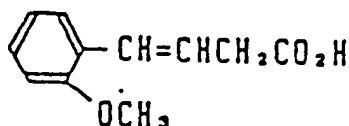
3.29(2H,d,J=5.7Hz), 6.34(1H,dt,J=5.7Hz,15.8Hz), 6.58(1H,d,J=15.8Hz), 7.3-7.7(4H,m), 9.84(1H,br)

(E)-4-(4-chlorophenyl)-3-butenic acido Fusing Point ($^{\circ}C$): 118.5 to 110o Value of Elemental Analysis: as $C_{10}H_9Cl_2$

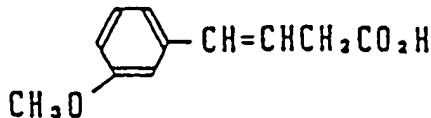
	C	H
Theoretical Value (%):	61.08	4.61
Observed Value (%):	61.12	4.67

o NMR($CDCl_3$) δ :

3.28(2H,d,J=6.0Hz), 6.19(1H,dt,J=6.0Hz,16.2Hz), 6.49(1H,d,J=16.2Hz), 7.1-7.4(4H,m), 11.32(1H,br)

(E)-4-(2-methoxyphenyl)-3-butenic acido NMR($CDCl_3$) δ :

3.31 (2H,dd,J=1.0Hz,7.0Hz) 3.86 (3H,s) 6.27 (1H,dt,J=7.0Hz, 16.3Hz) 6.7-7.5 (5H,m) 10.5 (1H,br)

(E)-4-(3-methoxyphenyl)-3-butenic acido Fusing Point ($^{\circ}C$): 96.5 - 97.5

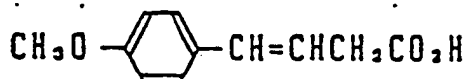
o Value of Elemental Analysis: as
C₁₁H₁₂O₃

	C	H
Theoretical Value (%)	68.74	6.29
Observed Value (%)	68.92	6.23

o NMR(CDCl₃) δ ;

3.29(2H,d,J=5.7Hz), 3.80(3H,s), 6.28(1H,dt,J=5.7Hz,15.8Hz), 6.45(2H,d,J=15.8Hz), 6.7-7.3(4H,m), 9.8-(1H,bs)

(E)-4-(4-methoxyphenyl)-3-butenic acid



o Fusing Point (°C): 102.5 - 104.5

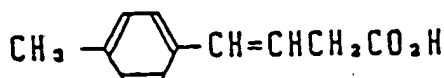
o Value of Elemental Analysis: As
C₁₁H₁₂O₃

	C	H
Theoretical Value (%)	68.73	6.30
Observed Value (%)	68.84	6.20

o NMR(CDCl₃) δ ;

3.26(2H,d,J=6.8Hz), 3.78(3H,s), 6.10(1H,dt,J=6.8Hz,16.6Hz), 6.45(1H,d,J=16.6Hz), 6.83(2H,d,J=8.6Hz), 7.30(2H,d,J=8.6Hz), 11.26(1H,br)

(E)-4-(4-methylphenyl)-3-butenic acid



o Fusing Point (°C): 113 - 114

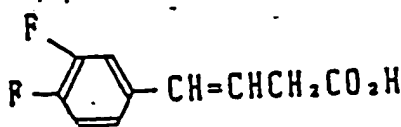
o Value of Elemental Analysis: as
C₁₁H₁₂O₂

	C	H
Theoretical Value (%)	74.97	6.87
Observed Value (%)	74.94	6.87

o NMR(CDCl₃) δ ;

2.32(3H,s), 3.27(2H,d,J=7.2Hz), 6.18(1H,dt,J=7.2Hz,16.2Hz), 6.49(1H,d,J=16.2Hz), 7.0-7.4(4H,m), 11.0-(1H,br)

(E)-4-(3,4-difluorophenyl)-3-butenic acid



5

o Fusing Point (°C): 95 - 96

10

o Value of Elemental Analysis: As C ₁₀ H ₈ F ₂ O ₂		
	C	H
Theoretical Value (%)	60.61	4.07
Observed Value (%)	60.85	4.02

15

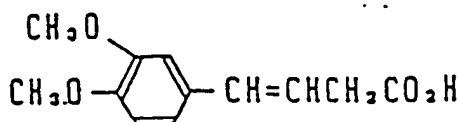
o NMR(CDCl₃) δ :

3.28 (2H,d,J=8Hz) 6.10 (1H,dt,J=8Hz,16Hz) 6.24 (1H,d,J=16Hz) 6.9 - 7.3 (3H,m)

20

(E)-4-(3,4-dimethoxyphenyl)-3-butenoic acid

25



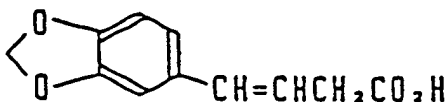
o NMR(CDCl₃) δ :

3.24(2H,d,J=6.5Hz), 3.82(3H,s), 3.84(3H,s), 6.06(1H,dt,J=6.5Hz,16.2Hz), 6.40(1H,d,J=16.2Hz), 6.8-7.0-(3H,m), 8.40(1H,br)

30

(E)-4-(3,4-methylenedioxyphenyl)-3-butenoic acid

35



40

o Fusing Point (°C): 114 - 115

45

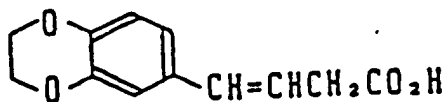
o Value of Elemental Analysis: As C ₁₁ H ₁₀ O ₄		
	C	H
Theoretical Value (%)	64.07	4.89
Observed Value (%)	64.28	4.95

50

o NMR(CDCl₃) δ : 3.22(2H,d,J=8Hz) 5.90(2H,s) 6.00(1H,dt,J=8Hz,16Hz) 6.36(1H,d,J=16Hz) 6.6 - 6.9-(3H,m)

55

(E)-4-(3,4-methylenedioxyphenyl)-3-butenoic acid

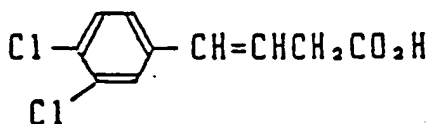


o Fusing Point (°C): 114 - 115

o Value of Elemental Analysis: as C ₁₁ H ₁₀ O ₄		
	C	H
Theoretical Value (%)	65.44	5.49
Observed Value (%)	65.56	5.61

o NMR(CDCl₃) δ : 3.20 (2H,d,J=8Hz) 4.18 (3H,s) 6.00(1H,dt,J=8Hz,16Hz) 6.32 (1H,d,J=16Hz) 6.6 - 6.9 (3H,m)

(E)-4-(3,4-dichlorophenyl)-3-butenoic acid

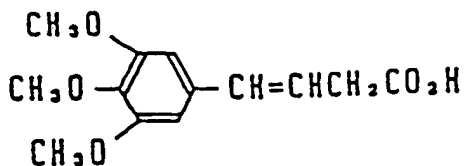


o Fusing Point (°C): 77 - 78

o Value of Elemental Analysis: As C ₁₀ H ₈ Cl ₂			
	C	H	Cl
Theoretical Value (%)	51.98	3.49	30.68
Observed Value (%)	52.21	3.47	30.57

o NMR(CDCl₃) δ : 3.30(2H,d,J=8.5Hz), 6.26(1H,dt,J=6.5Hz,15.8Hz), 7.1~7.5(3H,m), 9.8(1H,br)

(E)-4-(3,4,5-trimethoxyphenyl)-3-butenoic acid

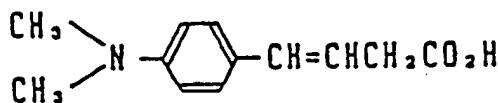


o Fusing Point (°C): 85 - 87

o Value of Elemental Analysis: as $C_{13}H_{14}C_5$		
	C	H
Theoretical Value (%):	61.89	6.39
Observed Value (%):	61.90	6.33

o NMR($CDCl_3$) δ : 3.26 (2H,d,J = 8Hz)
 3.80 (3H,S), 3.84 (6H,S) 6.08 (1H,dt,J = 8Hz,16Hz) 6.44 (1H,d,J = 16Hz) 6.56 (2H,S)

*(E)-4-(4-dimethylamino)phenyl)-3-butenolc acid

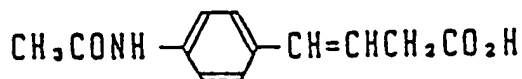


o Fusing Point ($^{\circ}C$): 203 - 204

o Value of Elemental Analysis: As $C_{12}H_{15}O_2N$			
	C	H	N
Theoretical Value (%)	70.22	7.37	6.82
Observed Value (%)	70.36	7.21	6.73

o NMR($CDCl_3$) δ ;
 2.94(6H,s), 3.25(2H,d,J = 7Hz), 6.00(1H,dt,J = -7Hz,16Hz), 6.40(1H,d,J = 16Hz), 6.55-6.75(2H,m), 7.16-7.35-(2H,m)

*(E)-4-(4-(acetyl amino)phenyl)-3-butenolc acid

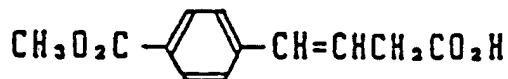


o Fusing Point ($^{\circ}C$): 216 - 217

o Value of Elemental Analysis: as $C_{12}H_{13}C_3N$			
	C	H	N
Theoretical Value (%):	65.74	5.98	6.39
Observed Value (%):	65.89	5.93	6.24

o NMR(DMSO) δ ;
 2.02(3H,s), 3.13(2H,d,J = 6Hz), 6.12(1H,dt,J = 6Hz,16Hz), 6.40(1H,d,J = 16Hz), 7.14-7.60(4H,m)

*(E)-4-(4-methoxycarbony)phenyl)-3-butenolc acid



5 o Fusing Point (°C): 118.5 - 121

10

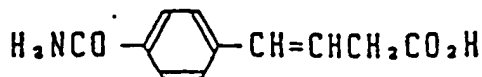
o Value of Elemental Analysis: As C ₁₂ H ₁₂ O ₄		
	C	H
Theoretical Value (%)	65.44	5.49
Observed Value (%)	65.65	5.42

15

o NMR(CDCl₃) δ ;
3.30(2H,d,J = 6.1Hz), 3.88(3H,s), 6.33(1H,dt,J = 6.1Hz,15.5Hz), 6.58(1H,d,J = 15.5Hz), 7.3-7.5(2H,m), 7.8-8.1-(2H,m), 9.45(1H,br)

20

*(E)-4-(4-carbamoyl)phenyl)-3-butenic acid



25

o Fusing Point (°C): 247 - 249

30

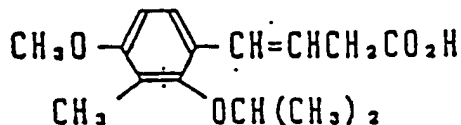
o Value of Elemental Analysis: as C ₁₁ H ₁₁ NO ₃			
	C	H	N
Theoretical Value (%):	64.38	5.40	6.83
Observed Value (%):	64.54	5.38	6.78

35

o NMR(DMSO-d₆) δ ;
3.20(2H,d,J = 5.8Hz), 6.34(1H,dt,J = 5.8Hz,15.8Hz), 6.66(1H,d,J = 15.8Hz), 7.1-7.6(3H,m), 7.6-8.1(3H,m)

40

*(E)-4-((2-isopropoxy-4-methoxy-3-methyl)phenyl)-3-butenic acid



45

o Fusing Point (°C): 116 - 117

50

o Value of Elemental Analysis: As C ₁₅ H ₂₀ O ₄		
	C	H
Theoretical Value (%)	68.16	7.63
Observed Value (%)	68.22	7.68

55

o NMR(CDCl₃) δ :

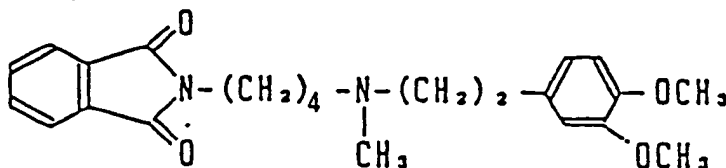
1.26(6H,d,J = 7Hz), 2.12(3H,s), 3.26(2H,dd,J = 1Hz,6Hz), 3.80(3H,s), 4.10(1H,heptet,J = 7Hz), 8.06-
(1H,dt,J = 6Hz,17Hz), 8.54(1H,d,J = 9Hz), 6.68(1H,d,J = 17Hz), 7.22(1H,d,J = 9Hz), 8.40(1H,br)

5 Manufacturing Examples 2

N-(2-(N'-methyl-N'-(2-(3,4-dimethoxyphenyl)ethyl)aminoethyl)phthalimide

10

15



20 8.08 g of hydroiodic acid of N-methyl-2-((3,4-dimethoxyphenyl)ethyl)amine, 8.46 g of N-(4-bromobutyl)phthalimide, 8.29 g of potassium carbonate and 50 ml of N,N'-dimethylformamide were mixed and the mixture was stirred at 80 °C for 4 hours. After completion of reaction the mixture was diluted with water and extracted with chloroform. After drying with sulfuric anhydride of magnesium, it was filtered and the solvent was distilled out. The residue was purified by means of silica gel column chromatography (solvent; chloroform : methanol = 100 : 1) and 9.44 g of the marked compound (yield: 95%) was obtained
25 as yellowish oily matter.

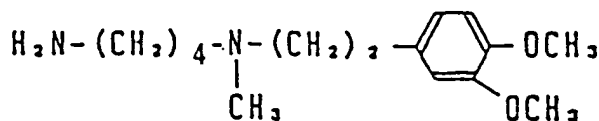
NMR (CDCl₃) δ :

1.3-1.9(4H,m), 2.2-2.9(9H,m) 3.65(2H,t,J = 6.8Hz), 3.78(3H,S), 3.81(3H,S) 6.5-6.9(3H,m), 7.5-7.9(4H,m)

30 Manufacturing Examples 3

N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-1,4-butanediamine

35



40

9.44 g of N-(4-(N'-methyl-N'-(3,4-dimethoxyphenyl)ethyl)amino)butyl)phthalimide as obtained in the manufacturing example 2 and 1.27 ml of monohydrate of hydrazine were dissolved into 50 ml of methanol and the solution was refluxed with heat for 2 hours. After cooling down to room temperature, the deposit
45 was filtered and the methanol was distilled off. To this was added aqueous solution of caustic soda and extraction was made with chloroform; then dried up with potassium carbonate anhydride. The solvent was distilled off and the residue was purified by means of silica gel column chromatography (solvent; chloroform : methanol : non-diluted aqueous ammonia = 100:10:1) and 5.21 g of the marked compound (yield: 82%) was obtained as yellowish oily matter.

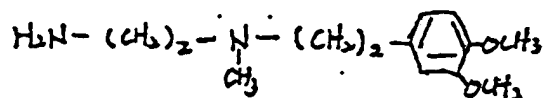
50 NMR (CDCl₃) δ :

1.3-1.8(4H, m) , 2.2-2.9 (11H,m) 3.26(2H,bs), 3.84 (3H,S) 3.87(3H,s), 6.5-6.9(3H,m)

The below shown compound was obtained in the same way as shown above.

N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-1,2-ethylenediamine (yellow oil),

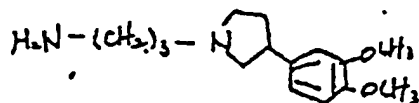
55 N-(3-aminopropyl)-3-(3,4-dimethoxyphenyl)pyrrolidine (yellow oil) and N-isopropyl-N-(2-phenylethyl)-1,3-propanediamine (yellow oil). They have the following formulae, respectively. Results of NMR analysis are shown, respectively.



5

NMR (CDCl₃) δ ; 1.75(2H,bs), 2.1-2.9(11H,m) 3.85(3H,s), 3.87(3H,S), 6.5-6.8(3H,m)

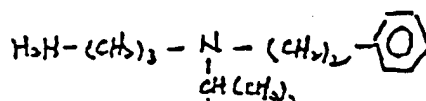
10



15

NMR (CDCl₃) δ ; 1.5-3.5 (15H,m) 3.83 (3H,S), 3.86 (3H,s) 6.76 (3H,S)

20

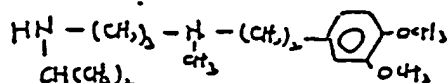


NMR (CDCl₃) δ ; 0.98 (3H,d,J=7Hz) 1.04 (3H,d,J=7Hz) 1.5- 1.8(2H,m) 2.1- 3.4(11H,m) 6.9-7.4(5H,m)

25 Manufacturing Example 4

N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-N'-isopropyl-1,3-propanediamine

30



35

3.87 g of N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-1,3-propanediamine and 15 ml of acetone were dissolved into 50 ml of ethanol. To this was added 0.1 g of platinum oxide and then hydrogenation was made at room temperature and under pressure of 3 kg/cm². At the end of 3 hours catalyst was concentrated after filtering and 4.52 g of marked compound was obtained as yellow oily matter (yield: 100%).

40

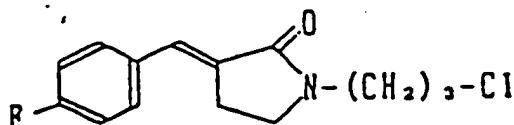
¹H NMR (CDCl₃) δ ; 1.06 (3H,d,J=7Hz) 1.5 - 1.9 (2H,m) 2.2 - 2.9 (13H, m) 3.83 (3H,S) 3.86 (3H,s) 6.6 - 6.9 (3H,m)

45 Manufacturing Examples 5

45

(E)-N-(3-chloropropyl)-3-(4-fluorobenzylidene-2-pyrrolidinone)

50



55

0.96 g of 60% sodium hydroxide, 2.58 ml of 1-chloro-3-iodopropane and 20 ml of N,N-dimethylformamide were mixed and the mixture was stirred at room temperature. To which 3.82 g of (E)-3-(4-

fluorobenzilidene)-2-pyrrolidinone dissolved into 20 ml of N,N-dimethylformamide was added dropwise and stirred for 3 hours. After completion of reaction, the product was put into ice water and extracted with ethyl acetate. After water washing, it was dried up with magnesium of sulfuric anhydride and the solvent was distilled off. The residue was purified by means of silica gel column chromatography (solvent; n-hexane : ethyl acetate = 3 : 2) and 3.55 g of the marked compound (yield: 66%) was obtained as white solid matter.

• NMR (CDCl₃) δ ;

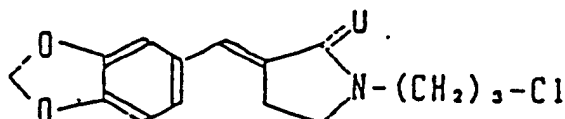
1.9 ~2.3(2H,m), 2.9~3.2(2H,m), 3.4~3.7(6H,m), 6.9~7.6(5H,m)

By the same method as above, the following compound was obtained

10

*(E)-N-(3-chloropropyl)-3-(3,4-(methylenedioxy)benzilidene)-2-pyrrolidinone

15



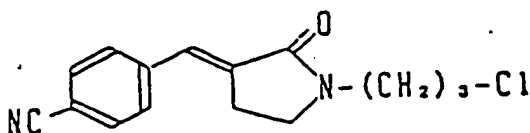
• Yellowish solid matter

• NMR (CDCl₃) δ ;

1.9 ~2.3(2H,m), 2.9~3.2(2H,m), 3.4~3.7(6H,m), 5.99(2H,s), 6.7~7.1(3H,m), 7.1 ~7.3(1H,m)

*(E)-N-(3-chloropropyl)-3-(4-cyanobenzilidene)-2-pyrrolidinone

25



30

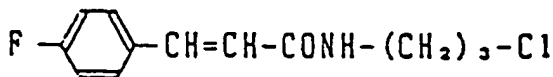
• NMR (CDCl₃) δ ;

35 1.9 ~2.3(2H,m), 2.9~3.2(2H,m), 3.4~3.8(6H,m), 7.2~7.4(1H,m), 7.4~7.8(4H,m)

Manufacturing Example 6

40

*(E)-N-(3-chloropropyl)-3-(4-fluorophenyl)propeneamide



45

Mixture of 4.15 g of 3-(4-fluorophenyl) propylenic acid, 2.37 ml of thionyl chloride and 20 ml of benzene was refluxed with heat for 3 hours. After concentration under reduced pressure, a coarse acid chloride was obtained. It was then dissolved into 20 ml of dichloromethane and the dissolved was added dropwise under incubation on ice into a mixture of 4.23 g of 3-chloropropylamine hydrochloric acid, 10.47 ml of N,N-diisopropylethylamine and 50 ml of dichloromethane. At the end of 1 hour, it was concentrated under reduced pressure. After dilution with water, extraction was effectuated with ethyl acetate. This was washed with diluted hydrochloric acid and saturated aqueous sodium bicarbonate, and then dried with magnesium of sulfuric anhydride. The solvent was distilled off and the residue was purified by silica gel column chromatography (solvent; n-hexane : ethyl acetate = 3 : 2) and 5.73 g of the marked compound (yield: 95%) was obtained as white solid.

55

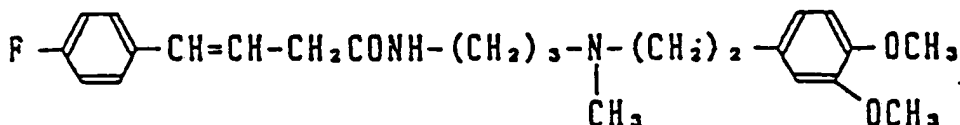
• NMR (CDCl₃) δ ;

1.9 ~2.3(2H,m), 3.3~3.7(4H,m), 6.20(1H,br), 6.32(1H,d,J = 15.8Hz), 6.8 ~7.1(2H,m), 7.2 ~7.7(3H,m)

Working Example 1(E)-N-(3-((N'-(2-(2,3-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-fluorophenyl)-3-buteneamide

5

10



15 A mixture of 30.0 g of (E)-4-(4-fluorophenyl)-3-butenoic acid, 14.6 ml of thionyl chloride and 350 ml of benzene was refluxed with heat for 2 hours. Concentration under reduced pressure gave a coarse acid chloride. It was dissolved into 200 ml of dichloromethane and the dissolved was then added dropwise, under incubation on ice, into a mixture of 47.1 g of N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-1,3-propanediamine, 26.3 g of potassium carbonate anhydride and 400 ml of dichloromethane. After 30 minutes the temperature was lowered down to room temperature and the mixture was stirred for 30 minutes. After completion of

20

25 reaction water was added, extraction was made with chloroform and drying applied with sulfuric anhydride of sodium. The solvent was distilled off and the residue was purified by means of silica gel column chromatography (solvent; chloroform : methanol = 25 : 1) and 55.3 g of the marked compound (yield: 79%) was obtained as yellow oily matter.

o NMR (CDCl₃) δ :

25

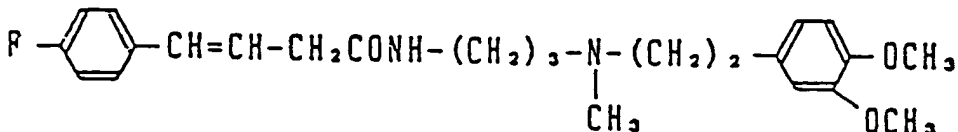
1.5 ~1.8(2H,m), 2.18(3H,s), 2.3~2.8(6H,m), 3.04(2H,d,J=6.8Hz), 3.2 ~3.5(2H,m), 3.84(3H,s), 3.86(3H,s), 6.12-(1H,dt,J=6.8Hz,15.2Hz), 6.48(1H,d,J=15.2Hz), 7.6~7.8(3H,m), 7.8~8.1(2H,m), 8.1 ~8.4(3H,m)

Working Example 2

30

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-fluorophenyl)-3-buteneamide dihydrochloride

35



40

• 2HCl

45 55.3 g of (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-fluorophenyl)-3-buteneamide as obtained under the working example 1 was dissolved into 100 ml of methanol, to which was added methanolhydrogen chloride. Further ether was added thereto to crystallize and 56.1 g of marked compound was obtained (yield: 86%) as slightly yellow powder.

o Fusing Point (°C): 101

50

o Value of Elemental Analysis: as C ₂₄ H ₃₃ FCl ₂ N ₂ O ₃					
	C	H	N	F	
Theoretical Value	59.13	6.82	5.75	3.89	(%)
Observed Value	59.13	6.83	5.80	3.91	(%)

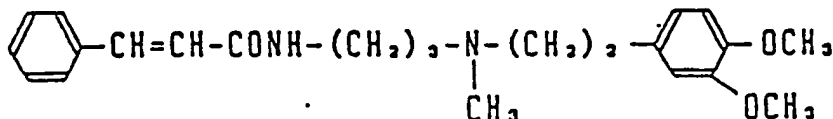
55

Working Example 3 - 69

The following compounds were produced by the same method as in the working example 1 above.

Working Example 3

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-methyl)amino)propyl))-3-phenylpropeneamide



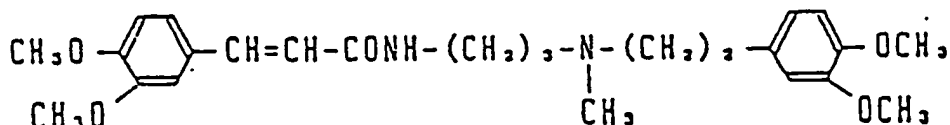
o Yellow oily matter

o NMR (CDCl₃) δ ;

1.5 -1.9(2H,m), 2.31(3H,s), 2.4-2.8(6H,m), 3.5 -3.6(2H,m), 3.76(3H,s), 3.84(3H,s), 6.18(1H,d,J=16Hz), 6.6-6.8(3H,m), 6.6 -6.8(3H,m), 7.0-7.6(7H,m)

Working Example 4

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(3,4-dimethoxyphenyl)propeneamide



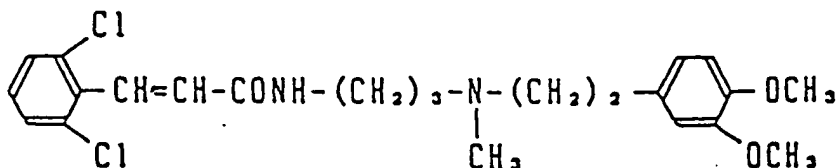
o Yellow oily matter

o NMR (CDCl₃) δ ;

1.6 -2.0(2H,m), 2.29(3H,s), 2.3-2.8(6H,m), 3.2 -3.5(2H,m), 3.76(3H,s), 3.78(3H,s), 3.81(6H,s), 6.44(1H,d,J=16Hz), 6.7-7.2(6H,m), 7.50(1H,d,J=16Hz)

Working Example 5

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(2,6-dichlorophenyl)propeneamide



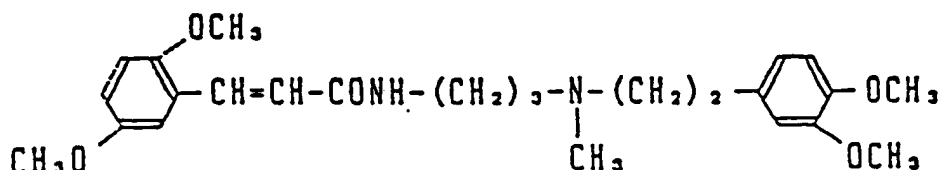
o Yellow oily matter

o NMR (CDCl₃) δ ;

1.6 -2.0(2H,m), 2.42(3H,s), 2.6-2.9(6H,m), 3.3 -3.6(2H,m), 3.80(3H,s), 3.84(3H,s), 6.40(1H,d,J=18Hz), 6.6-6.8(3H,m), 6.9 -7.8(5H,m)

Working Example 6

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(2,5-dimethoxyphenyl)propeneamide



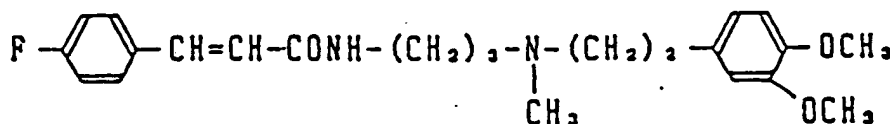
o Yellow oily matter

o NMR (CDCl₃) δ :

1.5 -1.9(2H,m), 2.30(3H,s), 2.4-2.8(6H,m), 3.2 -3.5(2H,m), 3.72(3H,s), 3.76(3H,s), 3.78(3H,s), 3.80(3H,s), 6.30(1H,d,J=18Hz), 6.6-7.3(8H,m), 7.7(1H,d,J=18Hz)

Working Example 7

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-fluorophenyl)propeneamide



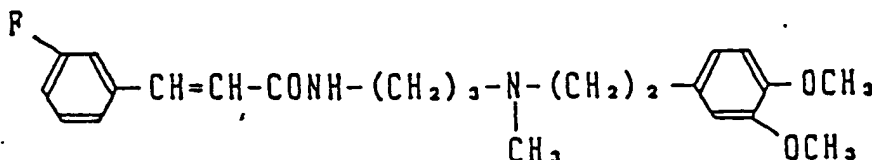
o Light yellowish oily matter

o NMR (CDCl₃) δ :

1.5 -1.9(2H,m), 2.28(3H,s), 2.3-2.8(6H,m), 3.3 -3.6(2H,m), 3.72(3H,s), 3.80(3H,s), 6.12(1H,d,J=18Hz), 6.72-6.8(3H,s), 6.8 -7.6(6H,m)

Working Example 8

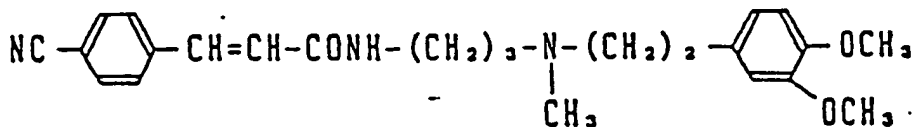
(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(3-fluorophenyl)propaneamide



o Yellow oily matter

o NMR (CDCl₃) δ :

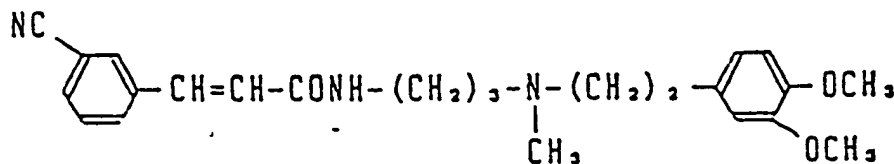
1.6 -1.9(2H,m), 2.34(3H,s), 2.4-2.9(6H,m), 3.3 -3.6(2H,m), 3.72(3H,s), 3.81(3H,s), 6.09(1H,d,J=14Hz), 6.6-6.8(3H,m), 6.8 -7.6(6H,m)

Working Example 9(E)-N-((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-cyanophenyl)propaneamide

o Light yellowish oily matter

o NMR (CDCl₃) δ :

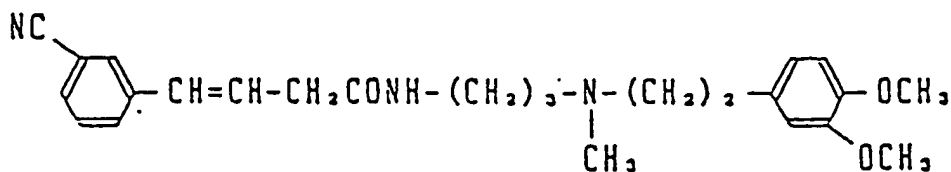
1.6 ~2.0(2H,m), 2.30(3H,s), 2.4~3.0(6H,m), 3.3 ~3.6(2H,m), 3.72(3H,s), 3.84(3H,s), 6.14(1H,d,J = 18Hz), 6.72-(3H,s), 7.2 ~7.9(6H,m)

Working Example 10(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-3-(3-cyanophenyl)propaneamide

o Yellow oily matter

o NMR (CDCl₃) δ :

1.6 ~1.9(2H,m), 2.30(3H,s), 2.4~2.8(6H,m), 3.3 ~3.6(2H,m), 3.69(3H,s), 3.81(3H,s), 6.20(1H,d,J = 15Hz), 6.68-(3H,s), 7.1 ~7.7(6H,m)

Working Example 11(E)-N-((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(3-cyanophenyl)-3-buteneamide

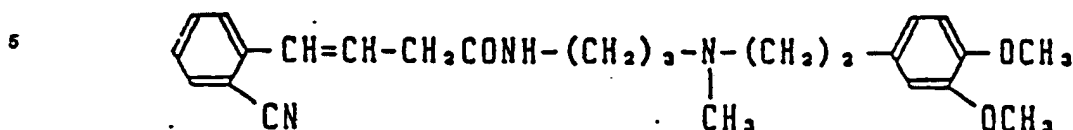
o Brown oily matter

o NMR (CDCl₃) δ :

1.5 ~1.9(2H,m), 2.14(3H,s), 2.4~2.8(6H,m), 3.02(2H,d,J = 6.8Hz), 3.2 ~3.5(2H,m), 3.84(3H,s), 3.86(3H,s), 6.1 ~6.9(5H,m), 7.1~7.7(5H,m)

Working Example 12

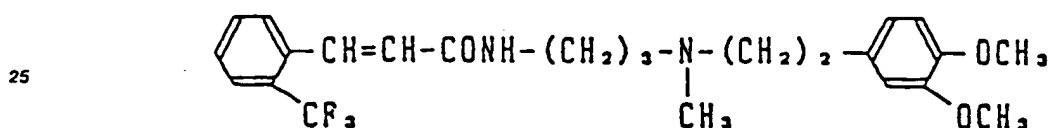
(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(2-cyanophenyl)-3-buteneamide



- 10
- o Yellow oily matter
 - o NMR (CDCl₃) δ ;
 - 1.5 ~1.9(2H,m), 2.13(3H,s), 2.4~2.8(6H,m), 3.06(2H,d,J = 6.8Hz), 3.2 ~3.5(2H,m), 3.82(3H,s), 3.86(3H,s), 6.48-
 - (1H,dt,J = 6.8Hz,16.2Hz), 6.7 ~6.9(4H,m), 7.1 ~7.7(5H,m)

15 Working Example 13

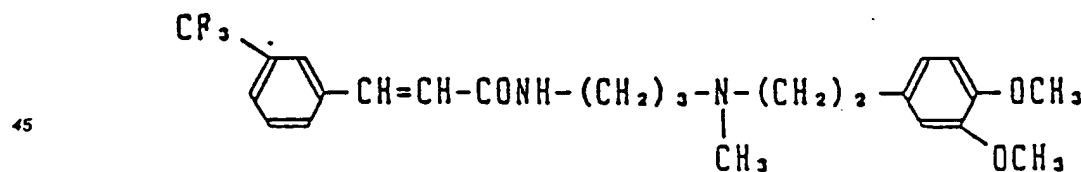
20 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(2-trifluorophenyl)phenyl)-propeneamide



- 30
- o Yellow oily matter
 - o NMR (CDCl₃) δ ;
 - 1.6 ~1.9(2H,m), 2.30(3H,s), 2.4~2.8(6H,m), 3.3 ~3.8(2H,m), 3.71(3H,s), 3.79(3H,s), 6.10(1H,d,J = 16Hz),
 - 6.6~6.8(3H,m), 7.2~7.8(6H,m)

35 Working Example 14

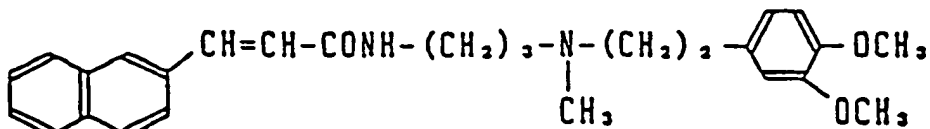
40 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(3-trifluorophenyl)phenyl)-propeneamide



- 50
- o Yellow oily matter
 - o NMR (CDCl₃) δ ;
 - 1.6 ~2.0(2H,m), 2.32(3H,s), 2.4~2.9(6H,m), 3.2 ~3.7(2H,m), 3.74(3H,s), 3.84(3H,s), 6.16(1H,d,J = 18Hz), 6.76-
 - (3H,s), 7.20(1H,br), 7.4~7.8(6H,m)

55 Working Example 15

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(2-naphthyl)propeneamide



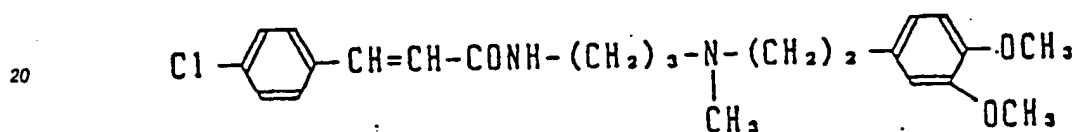
o Yellow oily matter

o NMR (CDCl₃) δ ;

10 1.7 -2.0(2H,m), 2.42(3H,s), 2.5-2.9(6H,m), 3.4 -3.9(2H,m), 3.71(3H,s), 3.76(3H,s), 6.30(1H,d,J = 16Hz), 6.76- (3H,s), 7.2(1H,br), 7.4 -8.0(8H,m)

Working Example 16

15 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-3-(4-chlorophenyl)propeneamide



o Yellow oily matter

25 o NMR (CDCl₃) δ ;

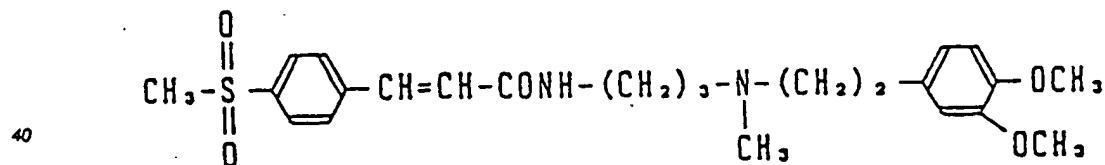
1.6 -1.9(2H,m), 2.34(3H,s), 2.4-2.9(6H,m), 3.3 -3.6(2H,m), 3.76(3H,s), 3.84(3H,s), 6.10(1H,d,J = 16Hz), 6.7-6.9(3H,m), 7.2(1H,br), 7.3 -7.6(5H,m)

Working Example 17

30

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-3-(4-methanesulphonylphenyl)propeneamide

35



o Yellow oily matter

45 o NMR (CDCl₃) δ ;

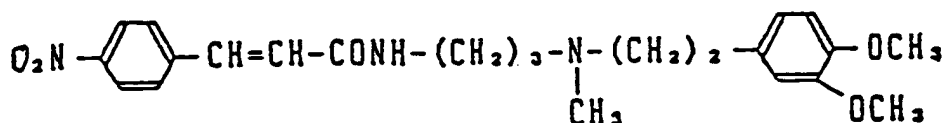
1.8 -2.0(2H,m), 2.38(3H,s), 2.4-2.9(6H,m), 3.08(3H,s), 3.3 -3.6(2H,m), 3.76(3H,s), 3.87(3H,s), 8.22- (1H,d,J = 16Hz), 6.7-6.8(3H,m), 7.36(1H,br), 7.4-7.7(3H,m), 7.8-8.0(2H,m)

Working Example 18

50

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-3-(4-nitrophenyl)propeneamide

55



5

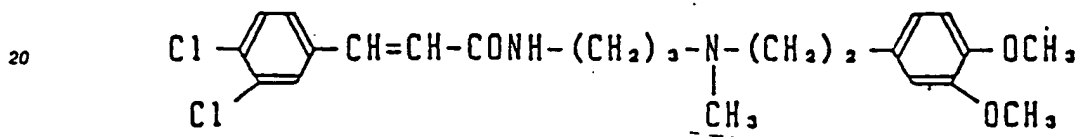
o Yellow oily matter

o NMR (CDCl₃) δ ;

1.5 -2.0(2H,m), 2.32(3H,s), 2.4-2.8(6H,m), 3.3 -3.6(2H,m), 3.71(3H,s), 3.82(3H,s), 6.10(1H,d,J=18Hz),
 10 6.6-6.8(3H,m), 7.2 -7.8(4H,m), 8.0-8.2(2H,m)

Working Example 19

15 (E)-N'-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(3,4-dichlorophenyl)-propeneamide



20

25

o Slightly yellow oil matter

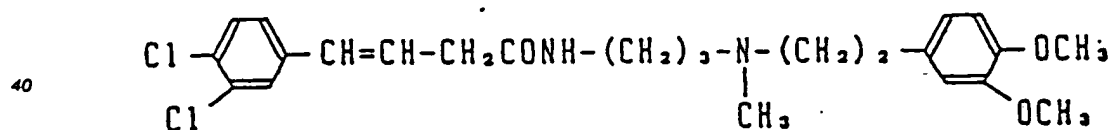
o NMR(CDCl₃) δ ;

1.6 -1.9(2H,m), 2.30(3H,s), 2.4-2.8(6H,m), 3.3 -3.6(2H,m), 3.72(3H,s), 3.82(3H,s), 6.02(1H,d,J=18Hz), 6.70-
 (3H,s), 7.1 -7.6(5H,m)

30

Working Example 20

35 (E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(3,4-dichlorophenyl)-3-buteneamide



40

45 o Yellow oily matter

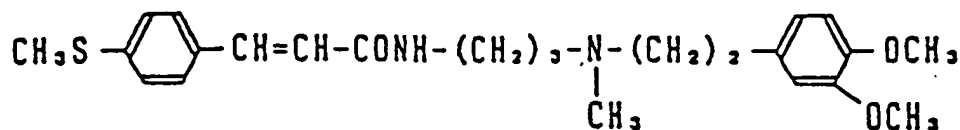
o NMR(CDCl₃) δ ;

1.5 -1.8(2H,m), 2.20 (3H,s), 2.4-2.8(6H,m), 2.99(2H,d, J=7Hz), 3.2 -3.5(2H,m) 3.82(3H,s), 3.84(3H,s), 6.18-
 (1H,dt, J=7Hz,16Hz), 6.38(1H,d, J=16Hz), 6.5 -6.9(3H,m), 7.0-7.4(4H,m)

50 Working example 21

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-methylthio)phenyl)-propeneamide

55



5

o White Crystal

o NMR(CDCl₃) δ ;

1.5 -1.9(2H,m), 2.32(3H,s), 2.4-2.9(9H,m), 3.2 -3.6(2H,m), 3.75(3H,s), 3.82(3H,s), 6.08(1H,d,J=16Hz),

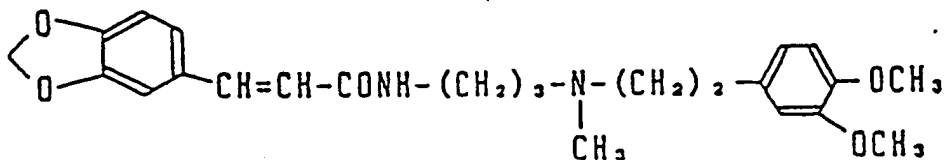
10

6.6-6.8(3H,m), 7.0 -7.7(6H,m)

Working Example 22

15 (E)-N-(((3-((N'-(2,3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-3(3,4-methylenedioxyphenyl)-propeneamide

20



25

o Yellow oily matter

o NMR(CDCl₃) δ ;

1.5 -2.0(2H,m), 2.32(3H,s), 2.4-2.8(6H,m), 3.2 -3.6(2H,m), 3.76(3H,s), 3.84(3H,s), 5.94(2H,s), 5.96-

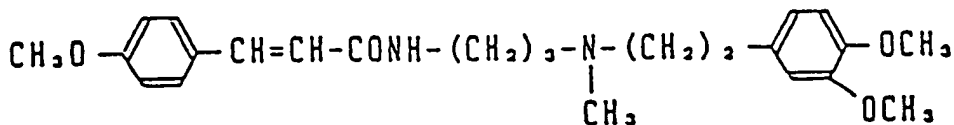
30

(1H,d,J=16Hz), 6.6-7.2(8H,m), 7.40(1H,d,J=16Hz)

Working Example 23

35 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-3-(4-methoxyphenyl)propeneamide

40



o Yellow oily matter

o NMR(CDCl₃) δ ;

45 1.6 -1.9(2H,m), 2.36(3H,s), 2.3-2.8(6H,m), 3.3 -3.6(2H,m), 3.76(3H,s), 3.80(3H,s), 3.82(3H,s), 6.06-

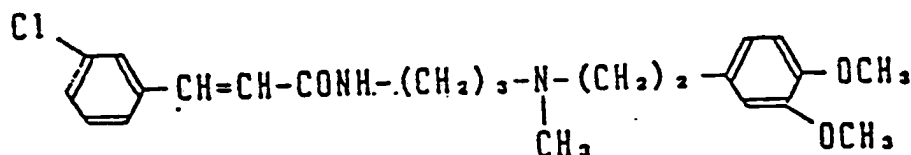
(1H,d,J=16)(Hz), 6.6-6.9(5H,m), 7.02(1H,br), 7.2 -7.6(3H,m)

Working Example 24

50

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-3-(3-chlorophenyl)propeneamide

55



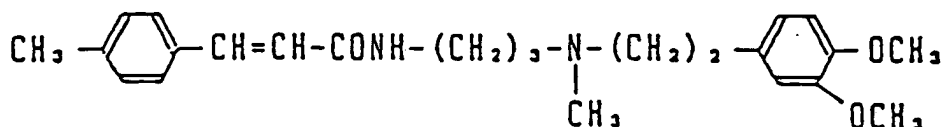
Yellow oily matter

o NMR(CDCl₃) δ ;

10 1.5 -2.0(2H,m), 2.32(3H,s), 2.4-2.8(6H,m), 3.2 -3.6(2H,m), 3.72(3H,s), 3.82(3H,s), 6.08(1H,d,J=16Hz), 6.6-6.8(3H,m), 7.1 -7.5(6H,m)

Working Example 25

15 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-methylphenyl)propeneamide



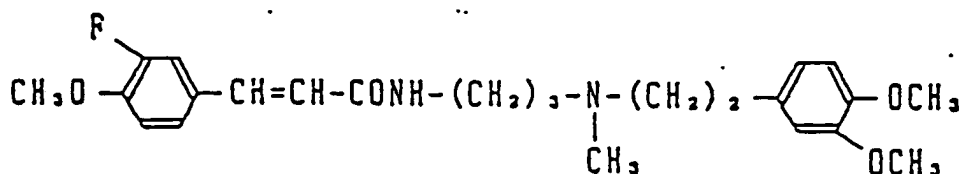
25 o Slightly yellowish oily matter

o NMR(CDCl₃) δ ;

1.5 -1.9(2H,m), 2.30(3H,s), 2.32(3H,s), 2.4 -2.8(6H,m), 3.3-3.6(2H,m), 3.74(3H,s) 3.82(3H,s), 6.16-(1H,d,J=17Hz), 6.8 -6.8(3H,m), 7.0-7.5(5H,m) 7.50(1H,d,Jd=17Hz)

30 Working Example 26

35 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(3-fluoro-4-methoxyphenyl)propeneamide



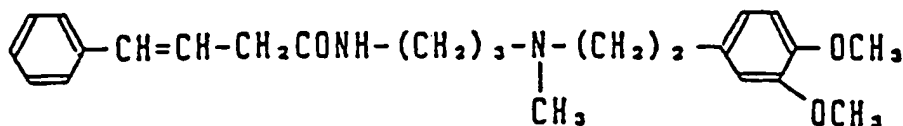
45 o Slightly yellowish matter

o NMR(CDCl₃) δ ;

1.5 -1.9(2H,m), 2.32(3H,s), 2.4-2.8(6H,m), 3.3 -3.6(2H,m), 3.78(3H,s), 3.86(3H,s) 3.92(3H,s), 6.00-(1H,d,J=17Hz), 6.7-7.5(7H,m), 7.46(1H,d,J=17Hz)

50 Working Example 27

55 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-phenyl)-3-buteneamide



5

o Yellow oily matter

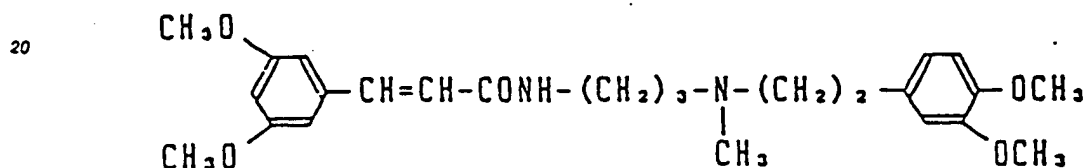
o NMR(CDCl₃) δ ;

1.5 -1.9(2H,m), 2.30(3H,s), 2.4-2.7(6H,m), 3.10(2H,d,J=8Hz), 3.2 -3.5(2H,m), 3.86(6H,s), 6.0 -6.5(2H,m),

10 6.5 - 6.9(3H,m), 7.0-7.5(6H,m)

Working Example 28

15 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(3,5-dimethoxyphenyl)-propeneamide



20

o Slightly yellowish matter

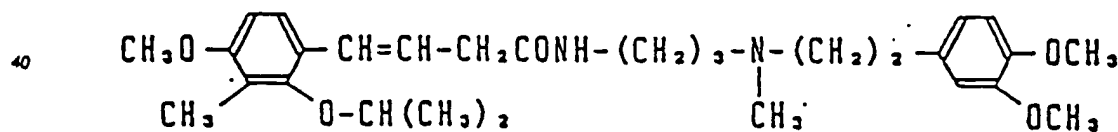
o NMR(CDCl₃) δ ;

1.5 -1.9(2H,m), 2.20(3H,m), 2.2-2.7(6H,m), 3.2 -3.5(2H,m), 3.66(9H,s), 3.72(3H,s), 6.16(1H,d,J=18Hz),

30 6.2-6.7(6H,m), 7.24(1H,br), 7.36(1H,d,J=18Hz)

Working example 29

35 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-((2-isopropoxy-4-methoxy-3-methyl)phenyl)-3-buteneamide



40

o Yellow oily matter

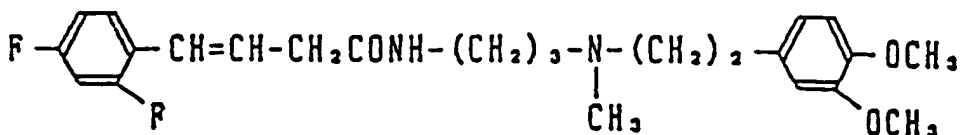
o NMR(CDCl₃) δ ;

1.28(6H,d,J=7Hz), 1.5 -1.9(2H,m), 2.10(3H,s), 2.20(3H,s), 2.3 -2.9(6H,m), 3.06(2H,d,J=6Hz), 3.2 -3.5(2H,m), 3.76(3H,s), 3.82(3H,s), 3.84(3H,s), 3.9 -4.3(1H,m), 6.04(, dt,J=6Hz,16Hz), 6.4 -6.9(5H,m), 7.04(1H,br), 8.23(1H,d,J=9Hz)

50

Working Example 30

55 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(2,4-difluorophenyl)-3-buteneamide



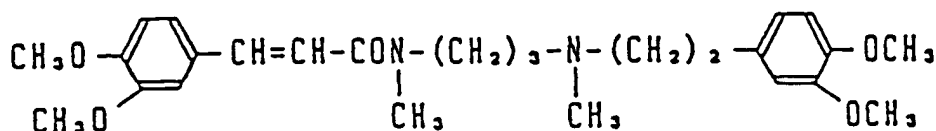
o Slightly yellowish oily matter

o NMR(CDCl₃) δ ;

10 1.5 -1.9(2H,m), 2.24(3H,s), 2.4-2.8(6H,m), 3.04(2H,d,J=6Hz), 3.1 -3.5(2H,m), 3.90(6H,s), 6.0 -6.5(2H,m), 6.5 -7.0(5H,m), 7.1-7.4(2H,m)

Working Example 31

15 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-methyl-3-(3,4-dimethoxyphenyl)propeneamide



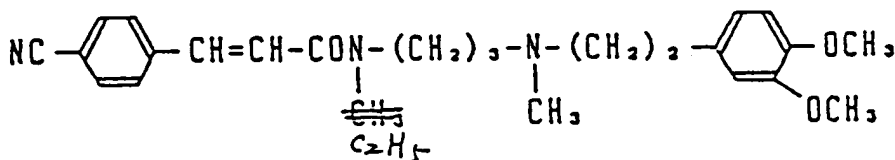
25 o Slightly yellowish oily matter

o NMR(CDCl₃) δ ;

30 1.7 -2.0(2H,m), 2.2-2.9(9H,m), 3.04, 3.16(total 3H,br s), 3.84(6H,s), 3.90(6H,s) 6.6 -7.2(7H,m) 7.66 (1H,d,J=16Hz)

Working Example 32

35 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-ethyl-3-(4-dicyanophenyl)propeneamide



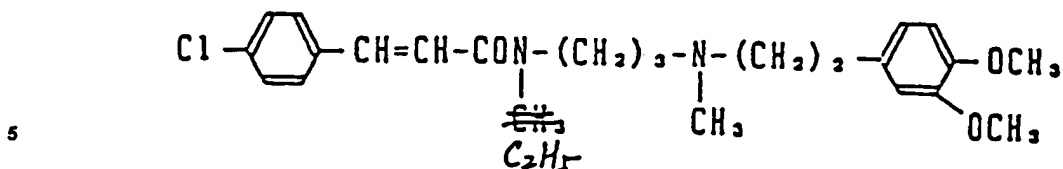
45 o Yellowish oily matter

o NMR(CDCl₃) δ ;

1.0 -1.4(3H,m), 1.6-2.0(2H,m), 2.30, 2.34(total 3H,s), 2.4 -2.8(6H,m), 3.2 -3.6(4H,m), 3.84(6H,s), 6.6-6.9(3H,m), 7.10(1H,d,J=18Hz), 7.5-7.8(5H,m)

Working Example 33

55 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-ethyl-3-(4-chlorophenyl)propeneamide



o Slightly yellowish oily matter

10 o NMR(CDCl₃) δ ;

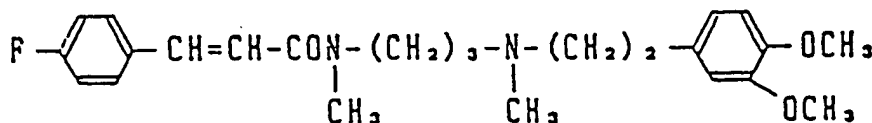
1.0 ~1.3(3H,m), 1.8~2.0(2H,m), 2.3(3H,br), 2.3~2.8(6H,m) 3.2~3.6(4H,m), 3.80(6H,s), 6.6 ~6.8(3H,m), 6.90(1H,d,J = 16Hz), 7.2~7.6(4H,m), 7.62(1H,d,J = 16Hz)

Working Example 34

15

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-N-methyl-3-(4-fluorophenyl)-propeneamide

20



25

o Yellow oily matter

o NMR(CDCl₃) δ ;

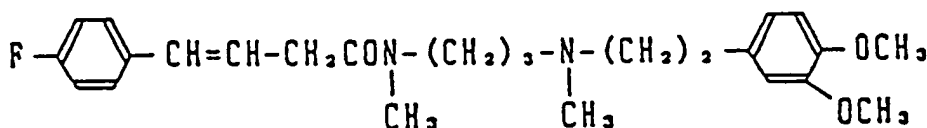
1.6 ~2.0(2H,m), 2.2~2.8(9H,m); 3.00, 3.10(total 3H,s), 3.3 ~3.6(2H,m), 3.80 (6H,s), 6.6 ~6.8(3H,m), 6.8~7.5- (6H,m)

30

Working Example 35

35 (E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-N-methyl-4-(4-fluorophenyl)-3-buteneamide

40



45

o Brown oily matter

o NMR(CDCl₃) δ ;

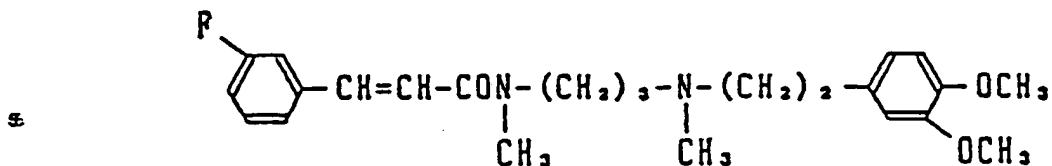
1.5 ~2.0(2H,m), 2.28,2.30(total 3H,s), 2.3 ~2.8(6H,m), 2.96(2H,d,J = 8Hz), 3.1 ~3.6(5H,m), 3.84(6H,s), 6.0~6.6(2H,m), 6.6 ~7.4(7H,m)

50

Working Example 36

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-N-methyl-3-(3-fluorophenyl)-propeneamide

55



o Yellow oily matter

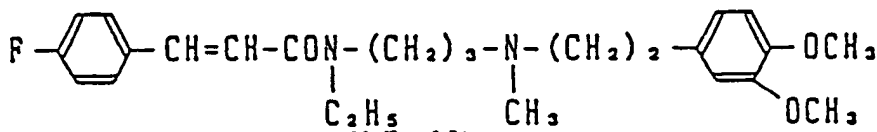
10 o NMR(CDCl₃) δ ;

1.5 ~2.0(2H,m), 2.4~2.9(9H,m), 3.00, 3.12(total 3H,s), 3.3 ~3.6(2H,m), 3.80(6H,s), 6.5 ~6.8(3H,m), 6.8~7.4 (5H,m), 7.46(1H,d,J=14Hz)

Working Example 37

15 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-ethyl-3-(4-fluorophenyl)-propeneamide

20



25

o Yellow oily matter

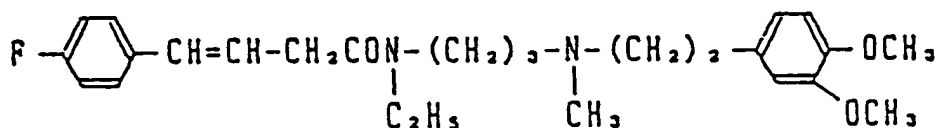
o NMR(CDCl₃) δ ;

30 1.17,1.24(total 3H,t,J=6Hz), 1.6~2.0(2H,m), 2.2 ~2.8(9H,m), 3.2~3.6(2H,m), 3.80(6H,s), 6.7 ~6.8(4H,m), 6.8~7.1(2H,m), 7.2 ~7.7(3H,m)

Working Example 38

35 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-ethyl-4-(4-fluorophenyl)-3-buteneamide

40



45

o Yellow oily matter

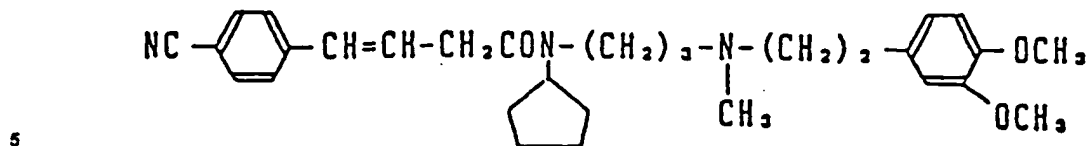
o NMR(CDCl₃) δ ;

1.10,1.16(total 3H,t,J=6Hz), 1.5~1.9(2H,m), 2.1 ~2.8(9H,m), 3.1~3.6(6H,m), 3.82(6H,s), 6.2 ~6.4(2H,m), 6.6~7.4(7H,m)

50

Working Example 39

55 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-cyclopentyl-4-(4-cyanophenyl)-3-buteneamide



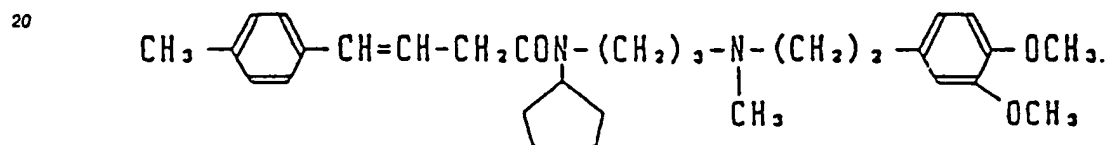
o Yellow oily matter

o NMR(CDCl₃) δ :

10 1.3 -2.0(10H,m), 2.2 -2.8(9H,m), 2.9 -3.4(4H,m), 3.80(3H,s), 3.82(3H,s), 3.9 -4.7(1H,br m), 6.2 -6.9(5H,m),
7.2 -7.8(4H,m)

Working Example 40

15 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-cyclopentyl-4-(4-methylphenyl)-3-buteneamide



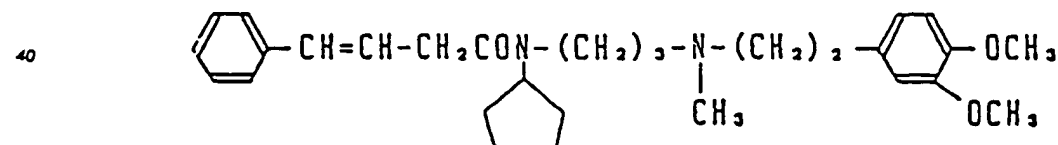
o Yellow oily matter

o NMR(CDCl₃) δ :

25 1.3 -2.0(10H,m), 2.2 -2.9(9H,m), 3.0 -3.4(4H,m), 3.80(3H,s), 3.82(3H,s), 3.9 -4.8(1H,br m) 6.20-
30 (1H,dt,J = 6Hz,16Hz), 6.40(1H,d,J = 16Hz), 6.5 -6.9(3H,m), 6.9 -7.3(4H,m)

Working Example 41

35 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-cyclopentyl-4-phenyl-3-buteneamide



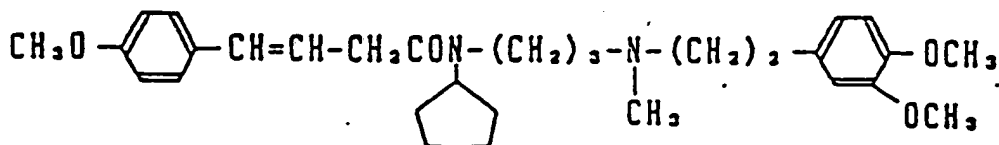
o Yellow oily matter

o NMR(CDCl₃) δ :

45 1.2 -2.0(10H,m), 2.2 -2.9(9H,m), 3.0 -3.4 (4H,m), 3.79(3H,s), 3.81(H,s), 3.9 -4.7(1H,br m), 6.20-
50 (1H,dt,J = 6Hz,16Hz), 6.44(1H,d,J = 16Hz), 6.6 -6.8(3H, m), 7.1 -7.5(5H,m)

Working Example 42

55 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-cyclopentyl-4-(4-methoxyphenyl)-3-butene amide



o Yellow oily matter

o NMR(CDCl₃) δ ;

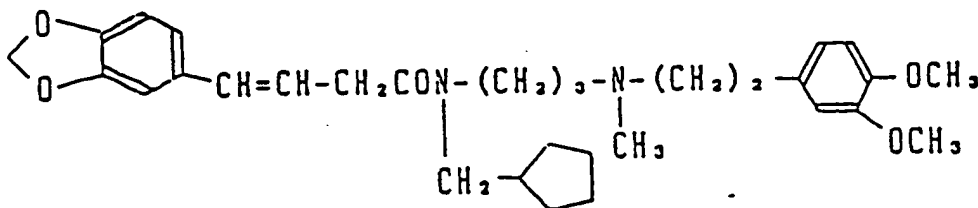
10 1.4 ~2.0(10H,m), 2.1 ~2.9(9H,m), 3.1 ~3.4(4H,m), 3.76(3H,s), 3.84(3H,s), 3.86(3H,s), 4.0 ~4.8(1H,br m), 6.16-
(1H,dt,J = 6Hz,16Hz), 6.41(1H,d,J = 16Hz), 6.6 ~7.0(5H,m), 7.2~7.4(2H,m)

Working Example 43

15

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-cyclopentylmethyl-4-(3,4-methylenedioxy)phenyl-3-buteneamide

20



25

o Yellow oily matter

30 o NMR(CDCl₃) δ ;

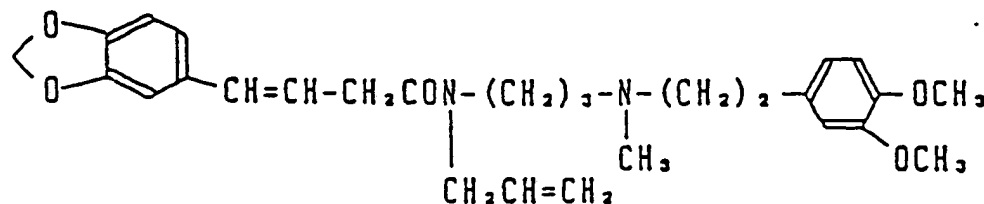
1.0 ~1.9(11H,m), 2.0 ~2.8(9H,m), 3.1 ~3.5(6H,m), 3.80(3H,s), 3.82(3H,s), 5.87(2H,s), 6.08-
(1H,dt,J = 6Hz,16Hz), 6.32(1H,d,J = 16Hz), 6.5~6.9(6H,m)

Working Example 44

35

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-aryl-4-(3,4-methylenedioxy)phenyl-3-buteneamide

40



45

50 o Yellow oily matter

o NMR(CDCl₃) δ ;

1.5 ~2.0(2H,m), 2.2~2.9(9H,m), 3.1~3.5(4H,m) 3.8~4.1(8H,m), 5.0~5.4(2H,m), 5.5 ~5.9(1H,m), 5.97(2H,s), 6.1
~6.6(2H,m), 6.6~7.0(6H,m)

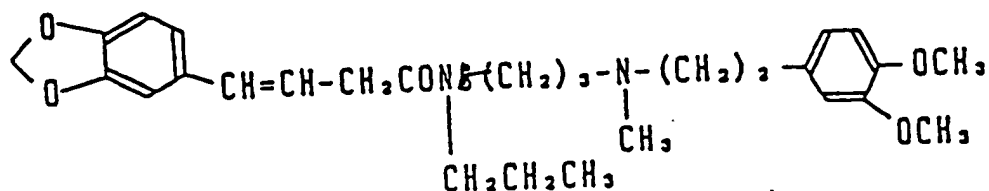
55

Working Example 45

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-propyl-4-(3,4-(methylenedioxy)-phenyl-3-buteneamide

5

10



o Yellow oily matter

15

o NMR(CDCl₃) δ ;

0.86,0.90(total 3H,t,J=7Hz), 1.3-1.9(4H,m), 2.1-2.8(9H,m), 2.9-3.5(6H,m), 3.80(3H,s) 3.82(3H,s), 5.86-5.88(2H,s), 6.08(1H,dt,J=6Hz,16Hz), 6.33(2H,d,J=16Hz), 6.5-6.9(6H,m)

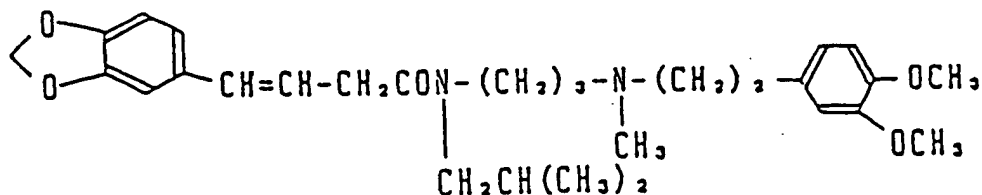
Working Example 46

20

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-(2-methylpropyl)-4-(3,4-(methylenedioxy)phenyl)-3-buteneamide

25

30



35

o Yellow oily matter

o NMR(CDCl₃) δ ;

1.04(3H,d,J=7Hz), 1.10(3H,d,J=7Hz), 1.5-2.1(3H,m), 2.2-2.8(9H,m), 2.9-3.5(6H,m), 3.78(3H,s), 3.80(3H,s), 5.94(2H,s), 6.08(1H,dt,J=6Hz,16Hz), 6.31(2H,d,J=16Hz), 6.5-6.9(6H,m)

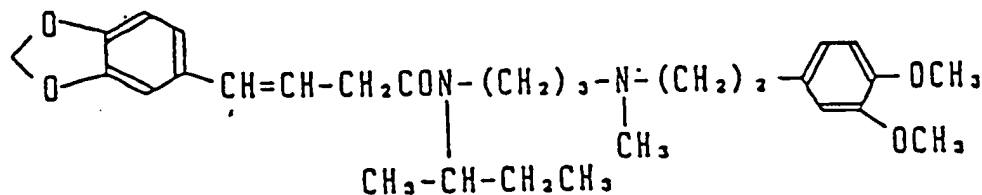
40

Working Example 47

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-(1-methylpropyl)-4-(3,4-(methylenedioxy)phenyl)-3-buteneamide

45

50



55

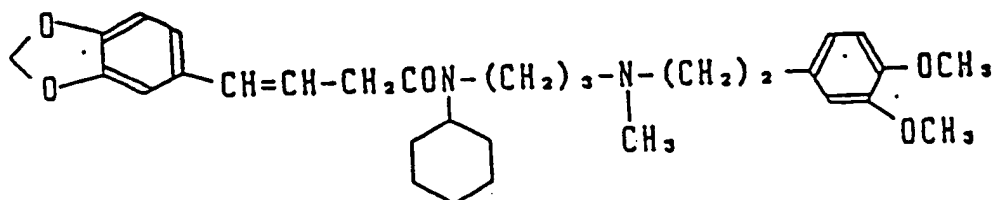
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.06,1.08(total 3H,d,J=7Hz), 1.08,1.20(total 3H,d,J=7Hz), 1.3 -2.0(4H,m), 2.3 -2.9(9H,m), 3.0-3.4(4H,m), 3.84(3H,s), 3.86(3H,s), 5.98(2H,s), 6.28(1H,dt,J=6Hz,16Hz), 6.40(1H,d,J=16Hz)

Working Example 48

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-cyclohexyl-4-(3,4-methylenedioxy)phenyl)-3-buteneamide

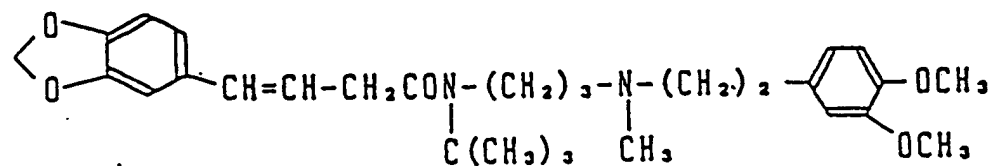


o NMR(CDCl₃) δ ;

0.9 -2.1(12H,m), 2.2 -2.9(9H,m), 3.1 -3.4(4H,m), 3.84(3H,s), 3.86(3H,s), 3.9 -4.4(1H,br), 5.92(2H,s), 6.1 -6.5(2H,m), 6.6 -7.0(6H,m)

Working Example 49

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-tert-butyl-4-(3,4-methylenedioxy)phenyl)-3-buteneamide



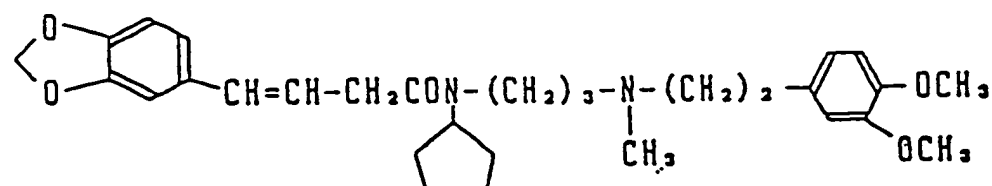
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.33(9H,s), 1.5 -1.9(2H,m), 2.2-2.9(9H,m), 3.1 -3.5(4H,m), 3.81(3H,s), 3.83(3H,s), 5.87(2H,s), 6.08-6.32(1H,dt,J=6Hz,16Hz), 6.32(1H,d,J=16Hz), 6.5-6.9(6H,m)

Working Example 50

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-isopropyl-4-(3,4-methylenedioxy)phenyl)-3-buteneamide



o Yellow oily matter

o NMR(CDCl₃) δ ;

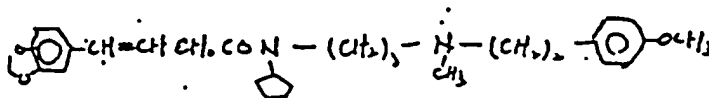
1.1 -2.0(10H,m), 2.2 -2.8(9H,m), 3.1 -3.4(4H,m), 3.86(3H,s), 3.88(3H,s), 3.9 -4.8(1H,bm), 5.92(2H,s), 6.16-
(1H,dt,J=6Hz,16Hz), 6.41(1H,d,J=16Hz), 6.8 -7.0(6H,m)

5

Working Example 51

10 (E)-N-(((3-(N'(2-(4-methoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-cyclopentyl-4-(3,4-(methylenedioxy)-
phenyl)-3-buteneamide

15



o Yellow oily matter

20 NMR(CDCl₃) δ ;

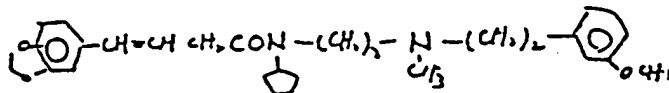
1.3 -2.0(10H,m), 2.3(3H,s), 2.3-2.84(6H,m), 3.0-3.32(4H,m), 3.72(3H,s), 3.9-4.5(1H,m), 5.86(2H,s), 6.1-
(1H,dt, J=6Hz,16Hz), 6.3(1H,d, J=16Hz); 6.6 -7.16(7H,m).

Working example 52

25

30 (E)-N-(((3-(N'(2-(3-methoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-N-cyclopentyl-4-(3,4-(methylenedioxy)-
phenyl)-3-buteneamide

30



35

o Yellow oily matter

NMR(CDCl₃) δ ;

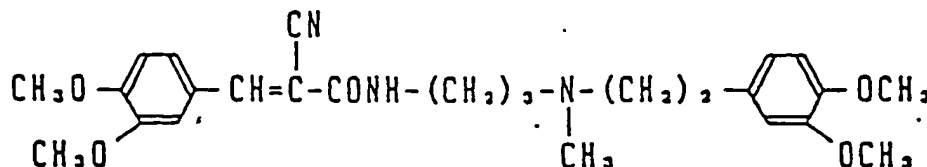
1.3-2.0(10H,m), 2.26(3H,s), 7.3-2.9(6H,m), 3.6-3.5(4H,m), 3.72(3H,s), 3.92-4.56(1H,m), 5.86(2H,s), 6.08(1H,
dt, J=6,16Hz), 6.32(1H,d,J=16Hz), 6.5-7.24(7H,m).

40

Working Example 53

45 (E)-N-(((3-(N'(2-(4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-2-cyano-3-(3,4-dimethoxyphenyl)-
propeneamide

50



55

o Yellow oily matter

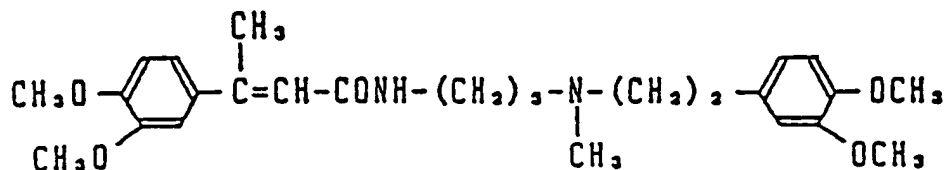
o NMR(CDCl₃) δ ;

1.6 -1.9(2H,m), 2.36(3H,s), 2.5-2.9(6H,m), 3.3 -3.6(2H,m), 3.76(3H,s), 3.82(3H,s), 3.90(6H,s), 6.68(3H,s).

6.82(1H,d,J = 8Hz), 7.40(1H,dd,J = 3Hz,8Hz), 7.64(1H,d,J = 3Hz), 8.12(1H,s), 8.76(1H,

Working Example 54

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-methyl-3-(3,4-(dimethoxyphenyl)-propeneamide)



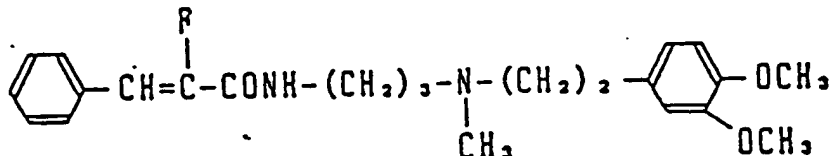
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.6 -2.0(2H,m), 2.02(3H,d,J = 2Hz), 2.36(3H,), 2.4 -2.9(6H,m), 3.3-3.6(2H,m), 3.78(3H,2), 3.80(3H,s), 3.82-(3H,s), 3.86(3H,s), 6.5 -6.8(3H,m), 6.8-7.0(3H,m), 7.08(1H,d,J = 2Hz), 7.60(1H,br)

Working Example 55

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-2-fluoro-3-phenyl)propeneamide



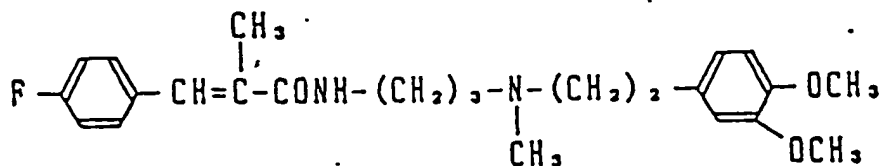
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.6 -2.0(2H,m), 2.32(3H,s), 2.4-2.9(6H,m), 3.3 -3.7(2H,m), 3.78(3H,s), 3.82(3H,s), 6.6 -6.8(3H,m), 7.0-7.7-(6H,m), 8.3(1H,br)

Working Example 56

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-2-methyl-3-(f-fluorophenyl)propeneamide



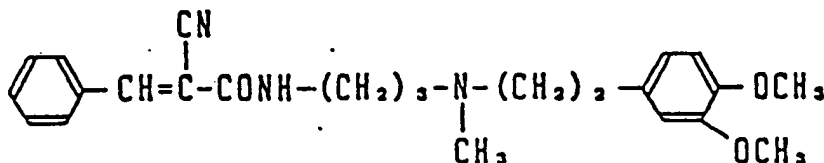
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.6 -1.9(2H,m), 1.96(3H,d,J=3Hz), 2.32(3H,s), 2.4 -2.8(6H,m), 3.3-3.6(2H,m), 3.88(3H,s), 3.91(3H,s), 6.5-6.8(3H,m), 6.8-7.4(5H,m), 7.70(1H,br)

Working Example 57

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-2-cyano-3-phenylpropeneamide



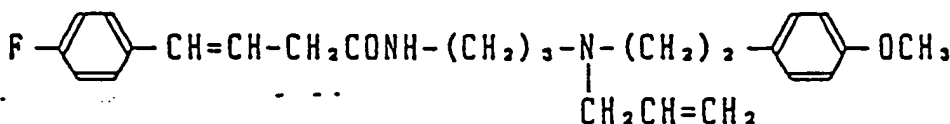
o Yellow oily matter

o NMR(CDCl₃) δ :

1.6 -1.9(2H,m), 2.3-2.9(9H,m), 3.3-3.6(2H,m), 3.78(3H,s), 3.84(3H,s), 6.74(3H,s), 7.4 -7.6(2H,m), 7.8-8.0(3H,m), 8.28(1H,s), 8.90(1H,br)

Working Example 58

(E)-N-(((3-((N'-(2-(4-dimethoxyphenyl)ethyl)-N'-aryl)amino)propyl)))-4-(4-fluorophenyl)-3-buteneamide



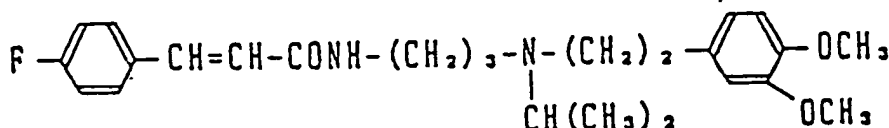
o Yellow oily matter

o NMR(CDCl₃) δ :

1.4 -1.8(2H,m), 2.5-2.7(6H,m), 2.9-3.2(4H,m), 3.2-3.5(2H,m), 3.76(3H,s), 5.0 -5.3(2H,m), 5.5-6.8(3H,m), 6.7-7.4(9H,m)

Working Example 59

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-isopropyl)amino)propyl)))-3-(4-fluorophenyl)propeneamide



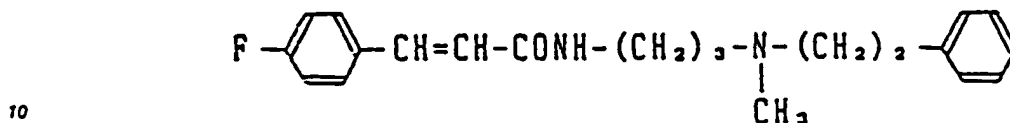
o Yellow oily matter

o NMR(CDCl₃) δ :

1.01(6H,d,J=7Hz), 1.5 -1.9(2H,m), 2.3 -2.9(6H,m), 2.9-3.3(1H,m), 3.3-3.6(2H,m), 3.75(3H,s), 3.85(3H,s), 8.04(1H,d,J=16Hz), 6.5-6.8(3H,m), 6.8-7.7(6H,m)

Working Example 60(E)-N-(((3-((N'-(2-phenylethyl)-N'-methyl)amino)propyl))-3-(4-fluorophenyl)propeneamide

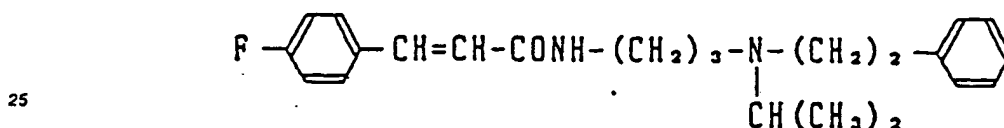
5



o White crystal

o NMR(CDCl₃) δ ;

15 1.5 -1.9(2H,m), 2.30(3H,s), 2.4-2.9(6H,m), 3.3 -3.6(2H,m), 5.99(1H,d,J = 16Hz), 6.8-7.6(11H,m)

Working Example 6120 (E)-N-(((3-((N'-(2-phenylethyl)-N'-isopropyl)amino)propyl))-3-(4-fluorophenyl)propeneamide

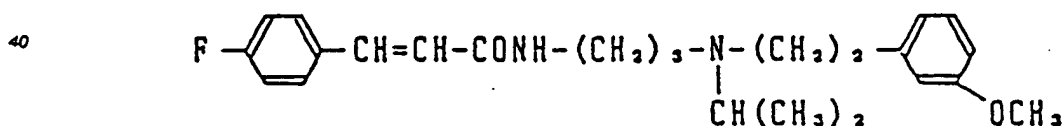
o Yellow oily matter

o NMR(CDCl₃) δ ;

30 0.99(6H,d,J = 7Hz), 1.5 -1.9(2H,m), 2.5 -2.8(6H,m), 2.9-3.3(1H,m), 3.3-3.6(2H,m), 5.99(1H,d,J = 16Hz), 6.9-7.6(11H,m)

Working Example 62

35

(E)-N-(((3-((N'-(2-(3-methoxyphenyl)ethyl)-N'-isopropyl)amino)propyl))-3-(4-fluorophenyl)propeneamide

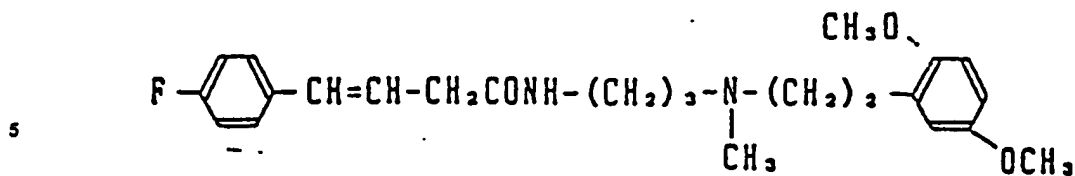
45 o Yellow oily matter

o NMR(CDCl₃) δ ;

1.02(6H,d,J = 7Hz), 1.5 -1.9(2H,m), 2.5 -2.9(6H,m), 2.9-3.3(1H,m), 3.3-3.6(2H,m), 3.75(3H,s), 6.00-(1H,d,J = 16Hz), 6.8 -7.7(10H,m)

50 Working Example 63(E)-N-(((3-((N'-(2-(2,5-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(4-fluorophenyl)-3-buteneamide

55



o Yellow oily matter

10 o NMR(CDCl₃) δ :

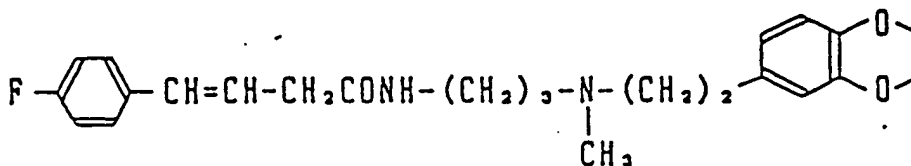
1.5 ~1.8(2H,m), 2.16(3H,s), 2.3~2.8(6H,m), 3.00(2H,d,J=8Hz), 3.2 ~3.5(2H,m), 3.74(6H,s), 5.9 ~6.6(2H,m), 6.0 ~7.6(8H,m)

Working Example 64

15

(E)-N-(((3-((N'-(2-(3,4-ethylenedioxy)phenyl)ethyl)-N'-methyl)amino)propyl))-4-(4-fluorophenyl)-3-buteneamide

20



25

o Slightly brownish oily matter

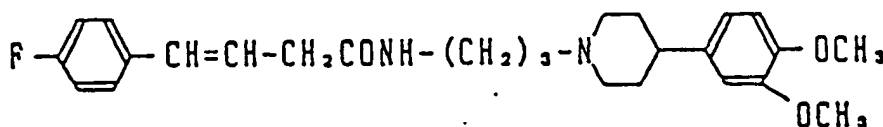
o NMR(CDCl₃) δ :

30 1.5 ~1.8(2H,m), 2.10 (3H,s), 2.3~2.6(6H,m), 2.96(2H,d,J=6Hz), 3.1 ~3.4(2H,m) 4.14(4H,s), 5.8 ~7.4(10H,m)

Working Example 65

35 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)piperidine-1-yl)propyl))-4-(4-fluorophenyl)-3-buteneamide

40



o Light yellow solid

45 o NMR(CDCl₃) δ :

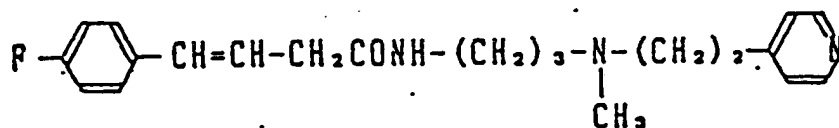
1.6 ~2.6(11H,m), 2.9 ~3.2(2H,m), 3.2 ~3.5(2H,m), 3.81(6H,s), 6.15(1H,dt,J=7Hz,16Hz), 6.44(1H,d,J=16Hz), 6.6 ~7.4

Working Example 66

50

(E)-N-(((3-((N'-(2-(4-pyridyl)ethyl)-N'-methyl)amino)propyl))-4-(4-fluorophenyl)-3-buteneamide

55



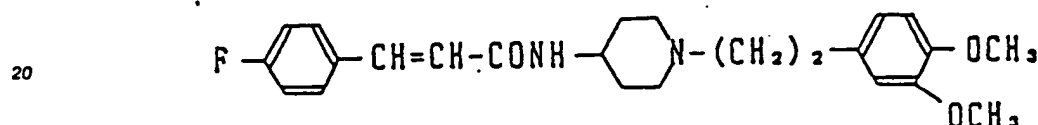
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.4 -1.8(2H,m), 2.15(3H,s), 2.3-2.7(6H,m), 3.00(2H,d,J=7Hz), 3.1 -3.5(2H,m), 6.04(1H,dt,J=7Hz,16Hz),
 10 6.36(1H,d,J=16Hz), 6.7-7.3(7H,m), 8.3-8.5(2H,m)

Working Example 67

15 (E)-N-(1-(2-(3,4-dimethoxyphenyl)ethyl)piperidine-4-yl)-3-(4-fluorophenyl)propenamide



o White solid

o NMR(CDCl₃) δ ;

1.3 -1.8(2H,m), 1.9-2.4(6H,m), 2.4-3.1(7H,m), 3.86(3H,s), 3.88(3H,s), 5.68(1H,d,J=8Hz), 6.32-
 25 (1H,d,J=16Hz), 6.6-6.9(3H,m), 6.9-7.2(2H,m), 7.3-7.7(3H,m)

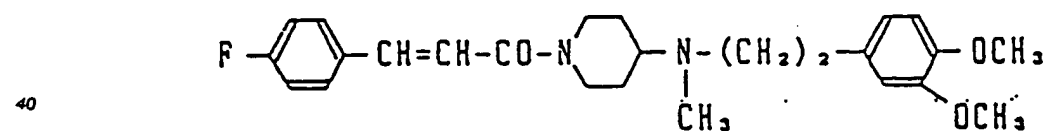
30 Working Example 68

(E)-N-(((4-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)piperidine

1-yl)-3-(4-fluorophenyl)-3-pro-

peneamide

35



o Light Yellow oily matter

o NMR(CDCl₃) δ ;

1.2 -2.1(4H,m), 2.36(3H,s), 2.5-3.2(7H,m), 3.87(3H,s), 3.89(3H,s), 6.6 -6.8(3H,m),
 45 6.9-7.3(4H,m), 7.4-7.8(3H,m)

Working Example 69

50 (E)-N-(((4-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)ethyl)-4-(4-fluorophenyl)-3-buteneamide



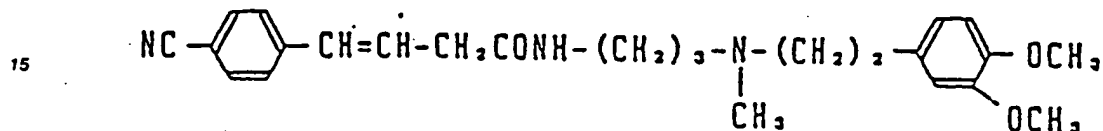
o Yellow oily matter

o NMR(CDCl₃) δ ;

2.28(3H,s), 2.4 -2.8(6H,m), 3.00(2H,d, J=7Hz), 3.1 -3.4(2H,m), 3.83(6H,s), 6.12(1H,br), 6.14-
 5 (1H,dt,J=7Hz,16Hz), 6.48(1H,d,J=Hz), 6.6-6.8(3H,m), 6.8 -7.1(2H,m), 7.2-7.4(2H,m) 6.35(1H,br), 6.49-
 (1H,d,J=16Hz), 6.6 -6.8(3H,m), 6.8-7.1(2H,m), 7.2-7.4(2H,m)

Working Example 70

10 (E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-4-cyanophenyl)-3-buteneamide



20 A mixture of 0.72 g of (E)-4-(4-cyanophenyl)-3-butenol acid, 1.07 g of N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-1,3-propanediamine, 0.87 g of N,N'-dicyclohexylcarbodiimide, 0.57 g of N-hydroxybenzotriazole and 13 ml of acetonitrile was stirred at 70 °C for 30 minutes.

It was then incubated to reduce the temperature. The deposit was filtered and concentrated.

25 To this was added water solution of potassium carbonate and extraction was performed with chloroform and then drying was applied with sodium sulfuric anhydride. The solvent was concentrated and the residue was purified by means of silica gel column chromatography(solvent; dichloromethane : methanol = 20 : 1) and the marked compound 1.52 g (yield:93 %) was obtained as yellow oily matter.

o NMR(CDCl₃) δ ;

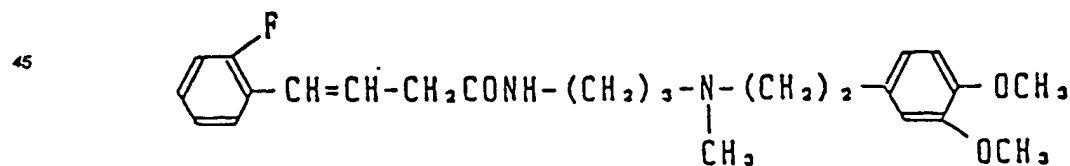
1.5 -1.8(2H,m), 2.14(3H,s), 2.4-2.8(6H,m), 3.01(2H,d,J=7Hz), 3.2 -3.5(2H,m), 3.84(3H,s), 3.88(3H,s), 6.1
 30 -6.5(2H,m), 6.6-6.8(3H,m) 7.1-7.0

Working Examples 71 - 95

35 The following compounds were produced by the same method as above.

Working Example 71

40 (E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(2-fluorophenyl)-3-buteneamide



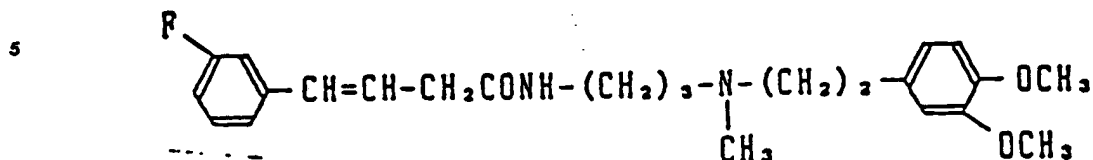
50 o Yellow oily matter

o NMR(CDCl₃) δ ;

1.5 -1.8(2H,m), 2.17(3H,s), 2.3-2.7(6H,m), 3.06(2H,d,J=7Hz), 3.2 -3.5(2H,m), 3.82(3H,s), 3.84(3H,s), 6.32-
 55 (1H,dt,J=7Hz,16Hz), 6.5 -6.8(4H,m), 6.9 -7.2(3H,m), 7.2-7.5(2H,m)

Working example 72

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(3-fluorophenyl)-3-buteneamide



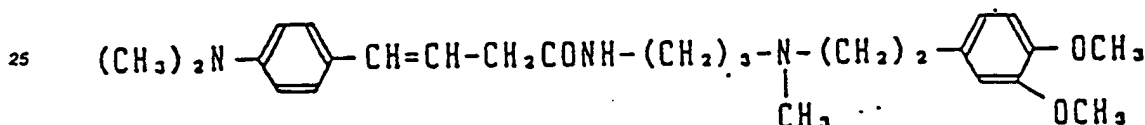
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.5 -1.8(2H,m), 2.18(3H,s), 2.3-2.7(6H,m), 3.02(2H,d,J = 7Hz), 3.2 -3.5(2H,m), 3.82(3H,s), 3.84(3H,s), 6.20-
15 (1H,dt,J = 7Hz,16Hz), 6.43(1H,d,J = 16Hz)6.8 -7.4(8H,m)

Working Example 73

20 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(4-dimethylamino)phenyl)-3-buteneamide



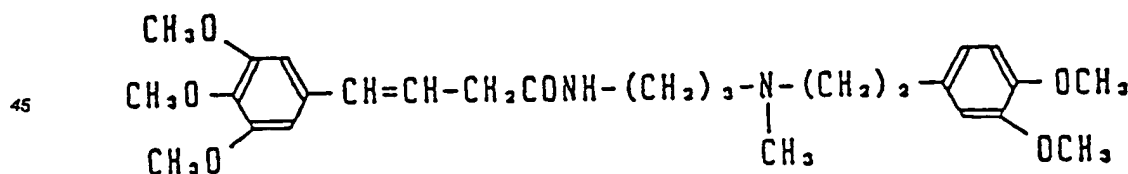
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.4 -1.8(2H,m), 2.16(3H,s), 2.2-2.8(6H,m), 2.93(6H,s), 3.03(2H,d,J = 7Hz), 3.1 -3.5(2H,m), 3.84(3H,s), 3.85-
35 (3H,s), 5.98(1H,dt,J = 7Hz, 16Hz), 6.32(1H,d,J = 16Hz), 6.4-6.8(5H,m), 7.0-7.3(3H,m)

Working Example 74

40 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(3,4,5-trimethoxyphenyl)-3-buteneamide



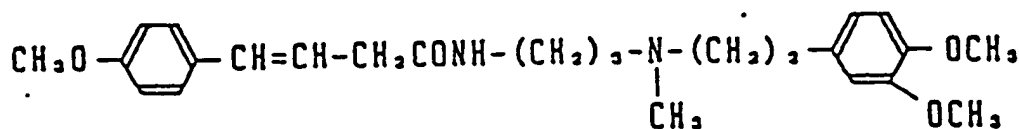
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.6 -1.9(2H,m), 2.28(3H,s), 2.4-2.8(6H,m), 3.04(2H,d,J = 6Hz), 3.2 -3.5(2H,m), 3.80(9H,s), 3.82(3H,s), 3.84-
55 (3H,s), 6.10(1H,dt,J = 6Hz,16Hz), 6.44(1H,d,J = 16Hz), 6.5-6.8(6H,m)

Working Example 75

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(4-methoxyphenyl)-3-buteneamide



5

o Yellow oily matter

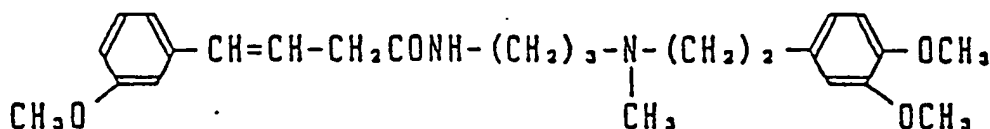
o NMR(CDC₃) δ :

10 1.5-1.8(2H,m), 2.18(3H,s), 2.3-2.7(6H,m), 3.03(2H,d,J=7Hz), 3.2-3.5(2H,m), 3.76(3H,s), 3.82(3H,s), 3.86-3.9(3H,s), 6.06(1H,dt,J=7Hz), 6.42(1H,d,J=16Hz), 6.6-6.9(5H,m), 7.2-7.4(3H,m)

Working example 76

15 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(3-methoxyphenyl)-3-buteneamide

20



25

o Yellow oily matter

o NMR(CDC₃) δ :

1.5-1.9(2H,m), 2.20(3H,s), 2.3-2.8(6H,m), 3.04(2H,d,J=6.2Hz), 3.1-3.5(2H,m), 3.75(3H,s), 3.83(3H,s), 3.85(3H,s), 6.25(1H,dt,J=6.2Hz,15.8Hz), 6.40(1H,d,J=15.8Hz), 6.5-7.4(8H,m)

30

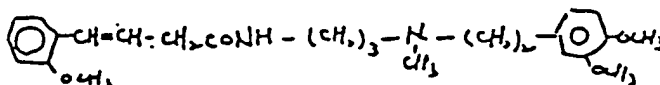
Working example 77

35 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)

amino)propyl))-4-(2-methoxyphenyl)-3-

buteneamide

35



40

o Yellow oily matter

o NMR(CDC₃) δ :

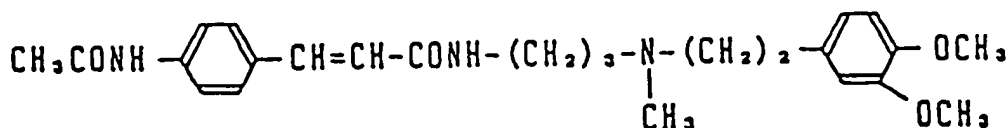
45 1.5-1.8(2H,m), 2.20(3H,s), 2.2-2.7(6H,m), 3.09(2HddJ = <1.0 and 7.0Hz), 3.2-3.5(2H,m), 3.76(3H,s), 3.84-3.9(3H,s), 6.25(1H,dt,J=7.0 and 18.0 Hz), 6.5-7.0(6H,m), 7.1-7.5(3H,m)

Working example 78

50 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-acetylamino)phenyl)-

propeneamide

55



o Yellow amorphous matter

o NMR(CDCl₃) δ ;

1.5 -1.9(2H,m), 2.16(3H,s), 2.32(3H,s), 2.4 -2.9(6H,m), 3.3-3.6(2H,m), 3.74(3H,s), 3.82(3H,s), 6.10-
(1H,d,J=16Hz), 6.6 -6.8(3H,m), 7.1-7.8(7H,m)

5

Working Example 79

10 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(4-(acetylamino)phenyl)-3-buteneamide



o Yellow oily matter

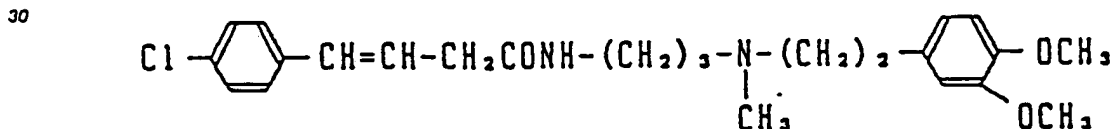
20 o NMR(CDCl₃) δ ;

1.6 -1.9(2H,m), 2.14(3H,s), 2.18(3H,s), 2.3 -2.8(6H,m), 2.96(2H,d, J=7Hz), 3.1 -3.4(2H,m), 3.81(3H,s), 3.84-
(3H,s), 6.01(1H,dt, J=7Hz,15Hz), 6.33(1H,d,J=15Hz), 6.4-6.8(3H,m), 6.9-7.6(7H,m), 8.82(1H,s)

25

Working Example 80

30 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(4-(chlorophenyl)-3-buteneamide



40

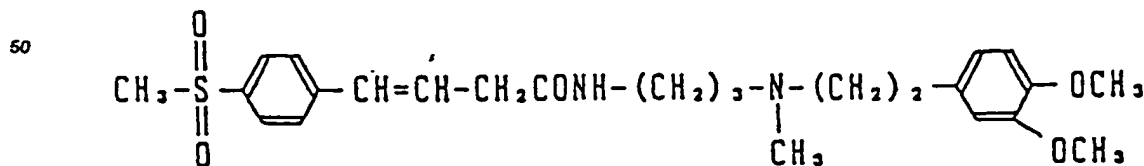
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.5 -1.8(2H,m), 2.18(3H,s), 2.4-2.8(6H,m), 3.02(2H,d,J=7Hz), 3.2 -3.5(2H,m), 3.82(3H,s), 3.86(3H,s), 6.16-
(1H,dt, J=7Hz,16Hz), 6.43(1H,d,J=16Hz), 6.6 -(3H,m), 7.1-7.4(5H,m)

Working Example 81

45 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(4-(methanesulfonyl)phenyl)-3-buteneamide



55

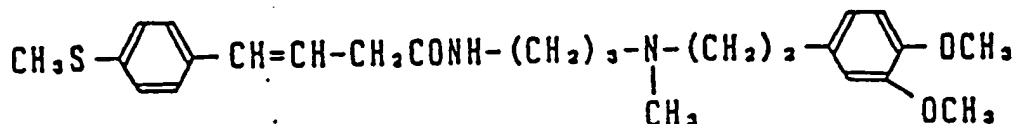
o Yellow oily matter

NMR(CDCl₃) δ ;

1.4 -1.9(2H,m), 2.22(3H,s), 2.3-2.8(6H,m), 3.00(3H,s), 3.02(2H,d, J = 4Hz), 3.1 -3.5(2H,m), 3.81(3H,s), 3.84(3H,s), 6.3 -6.9(5H,m), 7.0-7.9(5H,m)

Working Example 82

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(4-methylthio)phenyl)-3-buteneamide



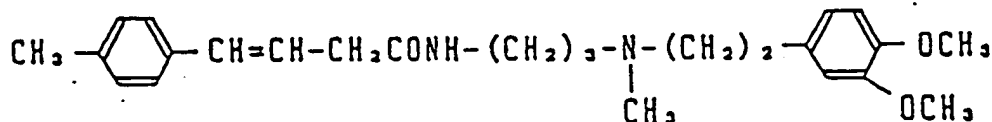
o Yellow oily matter

o NMR(CDCl₃) δ :

1.4 -1.8(2H,m), 2.17(3H,s) 2.3-2.8(9H,m), 3.03(2H,d,J=7Hz), 3.1 -3.4(2H,m), 3.84(3H,s), 3.85(3H,s), 5.9 -6.8(5H,m), 6.9-7.4(5H,m)

Working Example 83

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl) amino)propyl)))4-(4-methyl)phenyl)-3-buteneamide



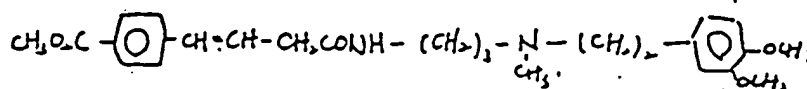
o Yellow oily matter

o NMR(CDCl₃) δ :

1.5 -1.8(2H,m), 2.17(3H,s), 2.31(3H,s), 2.4 -2.8(6H,m), 3.03(2H,d, J = 7Hz), 3.2 -3.5(2H,m), 3.83(3H,s)

Working Example 84

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))4-(4-methoxycarbonyl)phenyl)-3-buteneamide



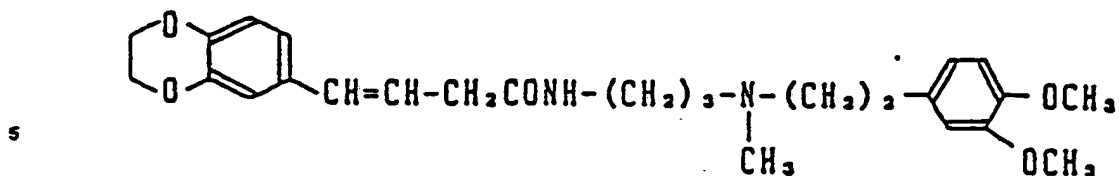
o Yellow oily matter

o NMR(CDCl₃) δ :

1.5-1.4(2H,m), 2.18(3H,s) 2.3-2.7(6H,m), 3.02(2H,d,J = 6Hz) 3.2-3.5(2H,m), 3.82(3H,s), 3.84(3H,s) 3.88(3H,s), 6.26(1H,dt, J = 6Hz,16Hz) 6.46 (1H,d, J = 16Hz, 6.5-6.8(3H,m) 7.1-7.5(3H,m) 7.8-8.0(2H,m)

Working Example 85

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl) amino)propyl)))4-(3,4-(ethylenedioxy)phenyl)-3-buteneamide



o slightly yellowish oily matter

10 o NMR(CDCl₃) δ ;

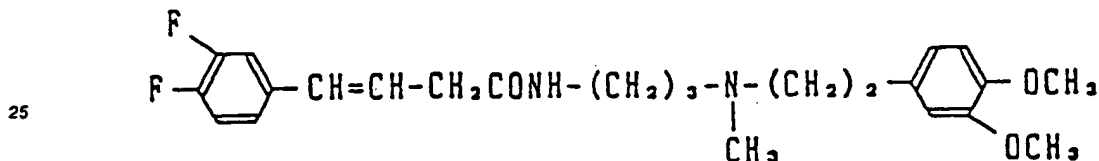
1.5 -1.8(2H,m), 2.16(3H,s), 2.4-2.7(6H,m), 3.02(2H,d,J=6Hz), 3.2 -3.5(2H,m), 3.92(3H,s), 3.94(3H,s), 4.18-4.18(4H,s), 5.8 -6.5(2H,m), 6.6-6.9(6H,m), 7.15(1H,br)

Working Example 86

15

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(3,4-(difluoro)phenyl)-3-buteneamide

20



o Slightly yellowish oily matter

30 o NMR(CDCl₃) δ ;

1.5 -1.8(2H,m), 2.22(3H,s), 2.3-2.8 (6H,m), 3.00(2H,d, J=6Hz), 3.1 -3.3 (2H,m), 3.84(3H,s), 3.88(3H,s), 6.10 (1H,dt, J=6Hz, 16Hz), 6.26(1H,d,J=16Hz), 6.3 -6.8(2H,m), 6.8-7.3(4H,m)

Working Example 87

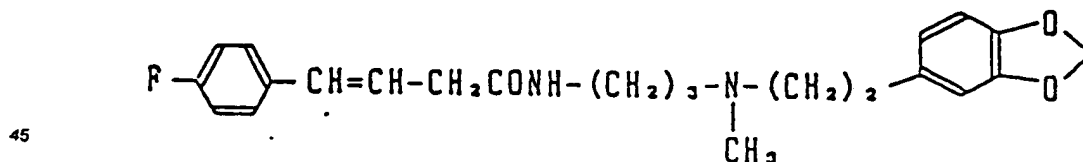
35

(E)-N-(((3-((N'-2-(3,4-methylenedioxy)phenyl)ethyl)-N'-methyl)

amino)propyl))-4-(4-(fluorophenyl)-3-

buteneamide

40



o slightly yellowish oily matter

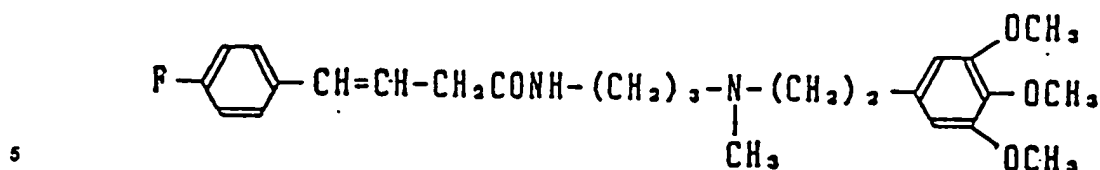
o NMR(CDCl₃) δ ;

50 1.5 -1.8(2H,m), 2.12(3H,s), 2.1-2.6(6H,m), 2.96(2H,d,J=8Hz), 3.1 -3.4(2H,m), 5.84(2H,s), 5.9 -7.4(10H,m)

Working Example 88

55

(E)-N-(((3-((N'-2-(3,4,5-trimethoxyphenyl)ethyl)-N'-methyl) amino)propyl))-4-(4-fluorophenyl)-3-buteneamide



o Yellowish brown oily matter

o NMR(CDCl₃) δ ;

10 1.5 -1.8(2H,m), 2.18(3H,s), 2.4-2.7(6H,m), 3.04(2H,d,J=8Hz), 3.2 -3.5(2H,m), 3.92(9H,s), 5.9 -6.5(4H,m),
6.8 -7.4(5H,m)

Working Example 89

15

(E)-N-(((3-((N'-(2-(4-methoxyphenyl)ethyl)-N'-methylamino)propyl))-4-(4-fluorophenyl)-3-buteneamide

20

25

o Slightly yellowish oily matter

o NMR(CDCl₃) δ ;

1.4 -1.8(2H,m), 2.12(3H,s), 2.2-2.7(6H,m), 2.96(2H,d, J=8Hz), 3.1 -3.5(2H,m), 3.70(3H,s), 5.8 -6.5(2H,m),
6.6 -7.4(9H,m)

30

Working Example 90

35

(E)-N-(((3-((N'-(2-(3,4-methylenedioxyphenyl)ethyl)-N'-methylamino)propyl))-4-(3,4-methylenedioxy)-phenyl)-3-buteneamide

40

45

o Slightly yellowish solid matter

o NMR(CDCl₃) δ ;

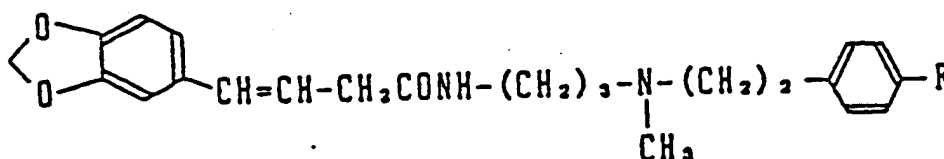
1.4 -1.8(2H,m), 2.16(3H,s), 2.4-2.6(6H,m), 3.00(2H,d,J=8Hz), 3.2 -3.5(2H,m), 5.90(2H,s), 5.92(2H,s), 6.0
-7.0(8H,m), 7.15(1H,br)

50

Working Example 91

55

(E)-N-(((3-((N'-(2-(4-fluorophenyl)ethyl)-N'-methylamino)propyl))-4-(3,4-methylenedioxy)phenyl)-3-buteneamide



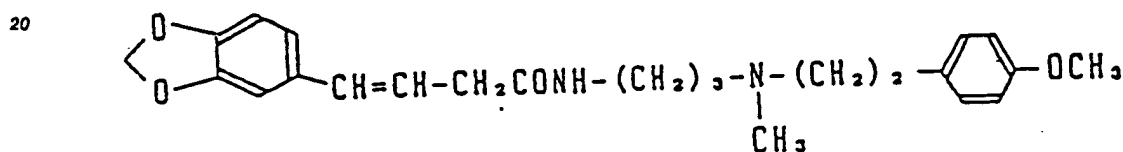
o Slightly yellowish solid matter

o NMR(CDCl₃) δ ;

10 1.5 -1.8(2H,m), 2.16(3H,s), 2.3-2.7(6H,m), 3.02(2H,d,J=8Hz), 3.2 -3.5(2H,m), 5.90(2H,s), 6.0 -6.6(2H,m), 6.6 -7.3(8H,m)

Working Example 92

15 (E)-N-(((3-((N'-(2-(4-methoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(3,4-methylenedioxy)phenyl)-3-butenamide



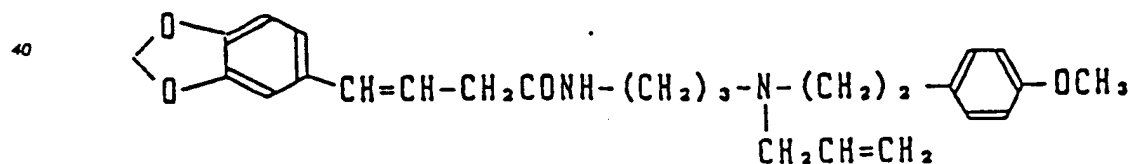
o Slightly yellowish solid matter

o NMR(CDCl₃) δ ;

25 1.5 -1.8(2H,m), 2.18(3H,s), 2.3-2.8(6H,m), 3.00(2H,d,J=8Hz), 3.2 -3.5(2H,m), 3.76(3H,s), 5.90(2H,s), 5.8 -6.5(2H,m), 6.8-7.3(8H,m)

Working Example 93

35 (E)-N-(((3-((N'-(2-(4-methoxyphenyl)ethyl)-N'-aryl)amino)propyl))-4-(3,4-methylenedioxy)phenyl)-3-butenamide



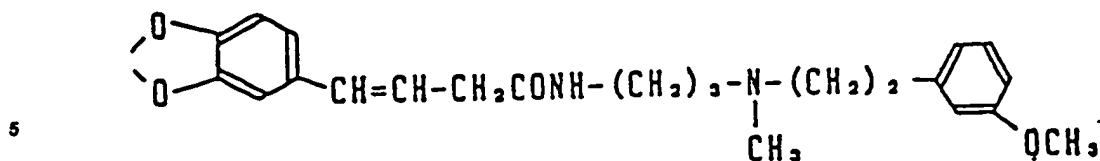
o Slightly brownish oily matter

o NMR(CDCl₃) δ ;

45 1.4 -1.8(2H,m), 2.4-2.7(6H,m), 2.9-3.2(4H,m), 3.1-3.5(2H,m), 3.76(3H,s), 5.0 -5.3(2H,m), 5.8-6.5(5H,m), 6.6-7.1(8H,m)

Working Example 94

55 (E)-N-(((3-((N'-(2-(3-methoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(3,4-methylenedioxy)phenyl)-3-butenamide



o Slightly brownish oily matter

10 o NMR(CDCl₃) δ ;

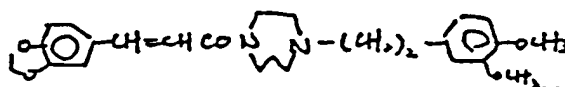
1.4 -1.8(2H,m), 2.14(3H,s), 2.3-2.7(6H,m), 2.94(2H,d,J=8Hz), 3.1 -3.5(2H,m), 3.72(3H,s), 5.7 -6.4(4H,m), 6.5 -7.2(8H,m)

Working Example 95

15

N-(((2-(3,4-dimethoxyphenyl)ethyl)-N'-(((E)-4-(3,4-(methylenedioxy)phenyl)-3-butenol)))))homopiperazine

20



25 o Yellow oily matter

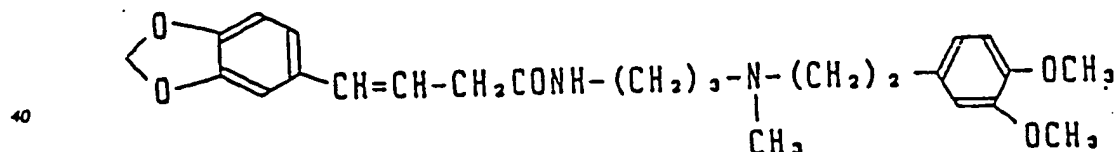
• NMR(CDCl₃) δ ;

1.73-2.08(2H,m), 2.49- 3.15(8H,m) 3.26(2H,d,J=7Hz), 3.35-3.78(4H,m) 3.85(3H,s), 3.87(3H,s), 5.93(3H,s) 6.16(1H,dt,J=15Hz,7Hz) 1.42(1H,d,J=15Hz) 6.57-6.90(6H,m)

30 Working Example 96

(E)-N-(((3-(((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-4-(3,4-methylenedioxy)phenyl)-3-butenamide

35



45 A mixture composed of 37.45 g of (E)-4-(3,4-(methylenedioxy)phenyl)-3-butenic acid, 23 g of N-hydroxysuccinimide and 800 ml of dichloromethane was incubated on ice and stirred. To this 41.3 g of N,N'-dicyclohexylcarbodiimide dissolved into 200 ml of dichloromethane was added dropwise for 1 hour. After 1.5 hour, 50 g of N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-1,3-propanediamine was added dropwise thereto for 30 minutes. After 5 hours the deposit was filtered and then the organic layer was washed with 0.5N aqueous hydrochloric acid. Then washing was conducted again with water and aqueous sodium carbonate followed by drying with magnesium sulfuric anhydride. The solvent was distilled off and the residue was purified by means of silica gel column chromatography (solvent; chloroform : methanol = 50 :

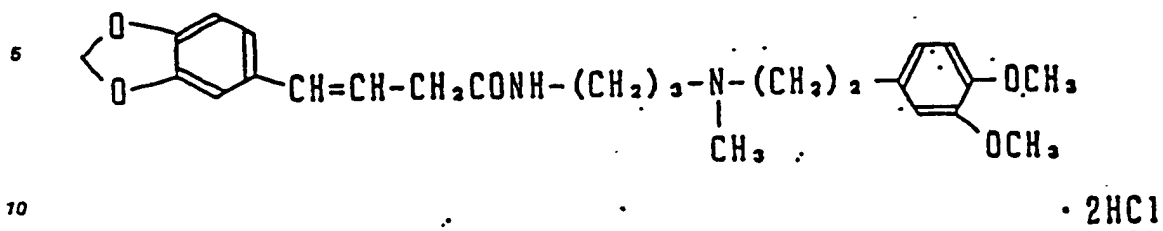
50 1 - 3) to obtain 70.36 g (yield: 88%) of marked compound.

o NMR(CDCl₃) δ ;

55 1.5 -1.9(2H,m), 2.28(3H,s), 2.4-2.8(6H,m), 3.04(2H,d,J=7Hz), 3.2 -3.5(2H,m), 3.84(3H,s), 3.86(3H,s), 5.90(2H,s), 6.00(1H,dt,J=7Hz,18Hz), 6.40(1H,d,J=18Hz), 6.6-7.0(6H,m), 7.2(1H,br)

Working Example 97

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)-

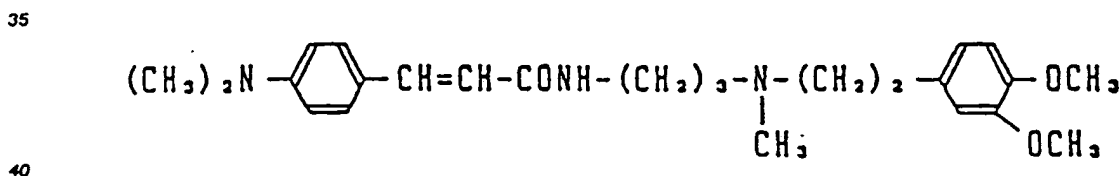


Into 150 ml of methanol was dissolved 72 g of the (E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)))-4-(3,4-(methylenedioxy)phenyl)-3-butenamine as obtained in the working example 93 hereabove. To this was added ethyl acetate-hydrogen chloride and then ethyl acetate. These were lubricated on ice and crystallized. The crystals were filtered and then recrystallized with ethanol-ethyl acetate to obtain 44 g of the marked compound (yield: 52%) as light yellow crystals.

20		o Value of Elemental Analysis: as			
		$C_{25}H_{34}Cl_2N_2O_2$			
			C	H	N
		Theoretical Value (%)	58.48	6.67	5.46
25		Observed Value (%)	58.27	6.51	5.37

Working Example 98

(E)-N-(((3-((N'-2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))3-(4-dimethylamino)phenyl)-propeneamide

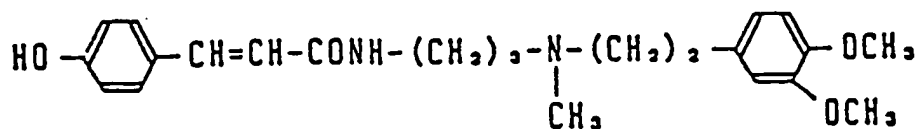


45 Into a mixture composed of 765 mg of (E)-3-(((4-(dimethylamino)phenyl))propylenic acid, 0.67 ml of triethylamine and 20 ml of tetrahydrofuran was added 0.64 ml of diethylchlorophosphate under incubation on ice and stirred for 1 hour. To this 1.0 g of N-methyl-N-(((2-(3,4-dimethoxyphenyl)ethyl)))1,3-propanediamine was added under incubation on ice and stirred for 2 hours. Water was added into reactive liquid, extraction was conducted with dichloromethane and dried up with magnesium sulfuric anhydride. The solvent was distilled off and the residue was purified by means of silica gel column chromatography (solvent; dichloromethane : ethanol = 9 : 1) to obtain 800 mg (yield: 47%) of the marked compound as yellow oily matter.

50 • NMR(CDCI₃) δ ;
1.56–1.9(2H,m), 2.74(3H,s), 2.3–2.9(6H,m), 3.00(6H,s), 3.3 –3.7(2H,m), 3.84(3H,s), 3.88(3H,s), 6.06–
(1H,d,J= 16Hz), 6.5–7.0(6H,m), 7.2–7.7(4H,m)

55 Working Example 99

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)))3-(4-hydroxyphenyl)propeneamide



5

A mixture composed of 0.82 g of (E)-3-(4-hydroxyphenyl)-propylenic acid, 1.68 ml of triethylamine and 5 ml of acetonitrile was cooled down to -10 °C and then stirred. To this was added dropwise 0.92 ml of ethylchloroformate and stirred for 30 minutes. Then was added dropwise thereto 3ml of acetonitrile solution of 3.02 g of N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-1,3-propanediamine and these were reacted at room temperature for 1 hour. Water was added thereto, extraction was conducted with chloroform and dried up with magnesium sulfuric anhydride. The solvent was distilled off and the residue was purified by means of silica gel column chromatography (solvent: chloroform : methanol = 10 : 1) to obtain 0.59 g (yield: 30%) of the marked compound as yellow amorphous matter.

15

• ¹H NMR(DMSO-d₆) δ ;

1.4 -1.8(2H,m), 2.20(3H,s), 2.3-2.8(6H,m), 3.0 -3.3(2H,m), 3.86(3H,s), 3.88(3H,s), 6.30(1H,d,J=16Hz), 6.6-6.8(5H,m), 7.1-7.5(3H,m), 7.85(1H,br)

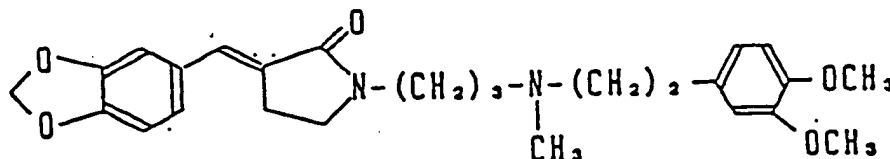
20

Working Example 100

25

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(3,4-methylenedioxy)benzilidene)-2-pyrrolidinone

30



35

A mixture composed of 1.17 g of (E)-N-(3-chloropropyl)-3-(3,4-(methylenedioxy)benzilidene)-2-pyrrolidinone, 1.55 g of N-methyl-(2-(3,4-dimethoxyphenyl)ethyl)amine hydroiodic acid, 1.33 g of potassium carbonate anhydride and 8 ml of N,N'-dimethylformamide was stirred to 90 °C for 5 hours. These were cooled down, water was added thereto, extraction was conducted with chloroform and then dried up with sodium sulfuric anhydride. The solvent was distilled off and the residue was purified by means of silica gel column chromatography (solvent: chloroform : methanol = 30 : 1) to obtain 1.69 g (yield: 93%) of the marked compound as yellow oily matter.

40

• NMR (CDCl₃) δ ;

1.5 -2.0(2H,m), 2.2-2.8(9H,m), 2.8-3.1(2H,m), 3.2 -3.6(4H,m), 3.83 (3H,s), 3.85(3H,s), 5.94(2H,s), 6.8-7.1-(6H,m), 7.1-7.4(1H,m)

45

Working Example 101 - 107

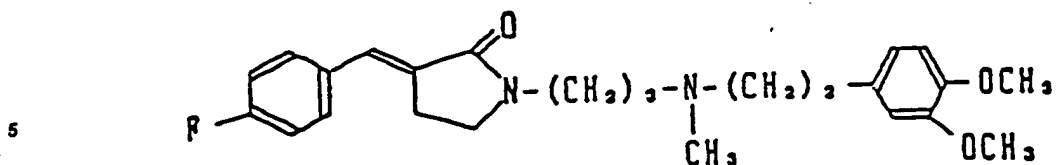
50

The following compounds were obtained by the same method as in Working Example 100.

Working Example 101

55

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-fluorobenzilidene)-2-pyrrolidinone



o Slightly yellowish oily matter

10 o NMR(CDCl₃) δ ;

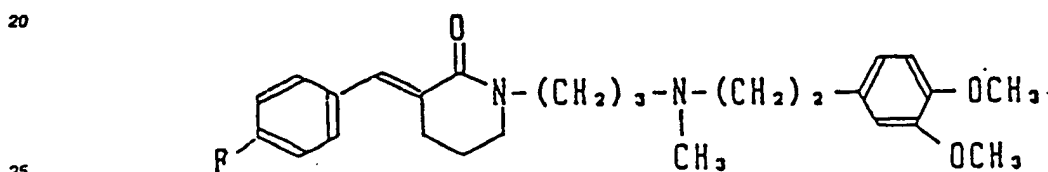
1.7 -2.1(2H,m), 2.40(3H,s), 2.4-3.0(6H,m), 3.0 -3.2(2H,m), 3.4-3.7(4H,m), 3.90(3H,s), 3.94(3H,s), 6.7-7.0-(3H,m), 7.0-7.6(5H,m)

Working Example 102

15

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)))-3-(4-fluorobenzilidene)-2-piperidone

20



25

o Slightly yellowish oily matter

o NMR(CDCl₃) δ ;

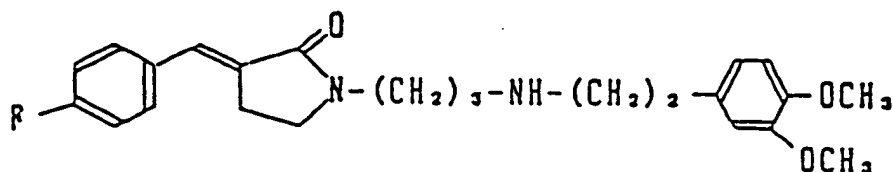
30 1.6 -2.0(4H,m), 2.32(3H,s), 2.3-2.8(8H,m), 3.2 -3.6(4H,m), 3.82(3H,s), 3.84(3H,s), 6.6 -6.8(3H,m), 6.9-7.4-(4H,m), 7.7(1H,s)

Working Example 103

35

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)amino)propyl)))-3-(4-fluorobenzilidene)-2-pyrrolidinone

40



45

o White solid matter

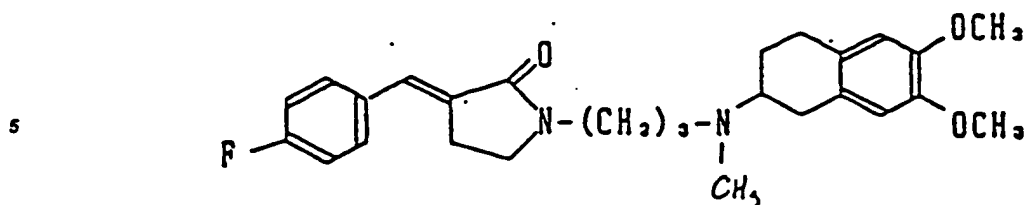
o NMR(CDCl₃) δ ;

50 1.7 -2.0(2H,m), 2.5-3.2(7H,m), 3.1-3.4(4H,m), 3.84(3H,s), 3.86(3H,s), 6.6 -6.9(3H,m), 6.9-7.6(5H,m)

Working Example 104

55

(E)-N-(((3-((N'-(2-(6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-yl)-N'-methyl)amino)propyl)))-3-(4-fluorobenzilidene)-2-pyrrolidinone



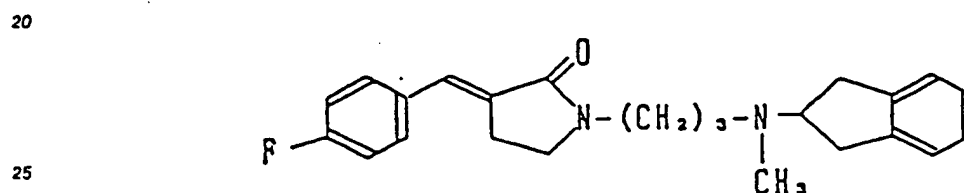
10 o Slightly brownish solid matter

o NMR(CDCl₃) δ :

1.5 -2.2(4H,m), 2.34(3H,s), 2.4-3.2(10H,m), 3.3 -3.7(4H,m), 3.83(6H,s), 6.56(2H,s), 6.9-7.6(5H,m)

15 Working Example 105

(E)-N-(((3-((N'-(indane-2-yl)-N'-methyl)amino)propyl))-3-(4-fluorobenzilidene)-2-pyrrolidinone



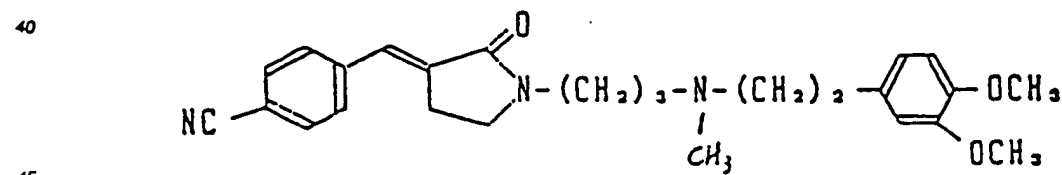
o Slightly brown solid matter

o NMR(CDCl₃) δ :

30 1.6 -2.0(2H,m), 2.27(3H,s), 2.3-2.6(2H,m), 2.6 -3.7(11H,m), 6.8 -7.6(9H,m)

Working Example 106

35 (E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-cyanobenzilidene)-2-pyrrolidinone



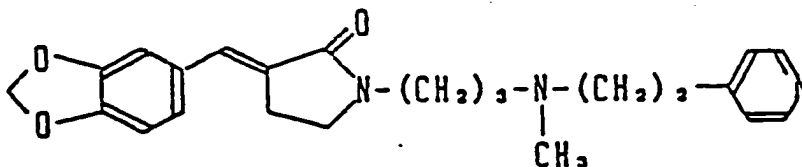
o Slightly brownish oily matter

o NMR(CDCl₃) δ :

50 1.6 -2.0(2H,m), 2.2-2.9(9H,m), 2.9-3.3(2H,m), 3.3-3.7(4H,m), 3.84(3H,s), 3.86(3H,s), 6.6-6.9(3H,m), 7.2-7.8(5H,m)

Working Example 107

55 (E)-N-(((3-((N'-(2-(4-pyridyl)ethyl)-N'-methyl)amino)propyl))-3-(3,4-(methylenedioxy)benzilidene)-2-pyrrolidinone



5

o Yellow oily matter

10 o NMR(CDCl₃) δ ;

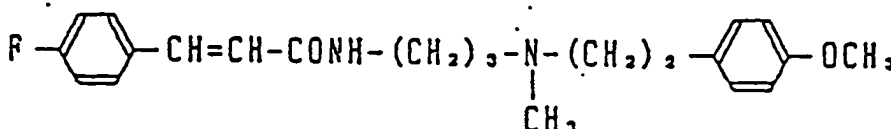
1.5 -1.9(2H,m), 2.2-3.2(11H,m), 3.3 -3.6(4H,m), 5.95(2H,s), 6.7-7.3(6H,m), 8.4 -8.6(2H,m)

Working Example 108

15

(E)-N-(((3-((N'-2-(4-methoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-fluorophenyl)propeneamide

20



25

A mixture composed of 0.6 g of (E)-N-(3-chloropropyl)-3-(4-fluorophenyl)propeneamide, 0.75 g of N-methyl-N-(2-(4-methoxyphenyl)ethyl)amine hydrochloric acid, 0.91 g of potassium carbonate anhydride, tetraiodine-n-butylammonium (volume in catalyst) and 5 ml of N,N'-dimethylformamide was stirred at 80 °C for 7 hours. These were cooled down, water was added thereto, and extraction was conducted with chloroform. After drying up with sodium sulfuric anhydride, the solvent was distilled off. Then the residue

30

o NMR(CDCl₃) δ ;

1.5 -1.9(2H,m), 2.34(3H,s), 2.4-2.9 (6H,m), 3.3-3.6(2H,m), 3.72(3H,s), 6.11(1H,d,J = 16Hz), 6.7-7.7(10H,m)

35

Working Example 109 - 120

The following compounds were obtained by the same method as in Working Example 108 above.

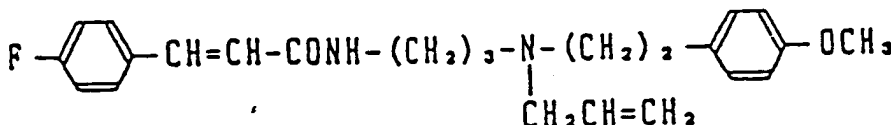
40

Working Example 109

45

(E)-N-(((3-((N'-2-(4-methoxyphenyl)ethyl)-N'-aryl)amino)propyl))-3-(4-fluorophenyl)propeneamide

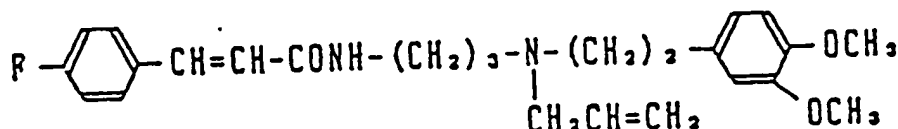
50



o Yellow oily matter

55 o NMR(CDCl₃) δ ;

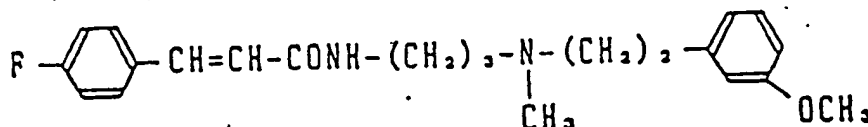
1.5 -1.9(2H,m), 2.5-2.8(6H,m), 3.10 (2H,d,J = 7Hz), 3.2 -3.5(2H,m), 3.62 (3H,s), 5.0 -5.3(2H,m), 5.5-6.1-(2H,m), 6.6 -7.6(10H,m)

Working Example 110(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-aryl)amino)propyl))-3-(4-fluorophenyl)propeneamide

o Yellow oily matter

o NMR(CDCl₃) δ :

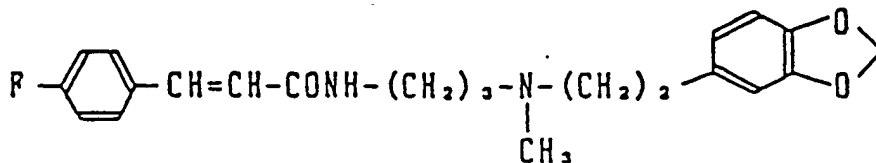
1.5 -1.9(2H,m), 2.5-2.9(6H,m), 3.14 (2H,d,J=7Hz), 3.3 -3.6(2H,m), 3.76 (3H,s), 3.84(3H,s), 5.0 -5.4(2H,m), 5.6-6.0(1H,m), 6.10(1H,d,J=16Hz), 6.73(3H,s) 6.9 -7.6(6H,m)

Working Example 111(E)-N-(((3-((N'-(2-(3-methoxyphenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-fluorophenyl)propeneamide

o Yellow oily matter

o NMR(CDCl₃) δ :

1.5 -1.9(2H,m), 2.29(3H,s) 2.4 -2.8(6H,m), 3.3 -3.5(2H,m), 3.72(3H,s), 5.98(1H,d,J=16Hz), 6.6 -7.8(10H,m)

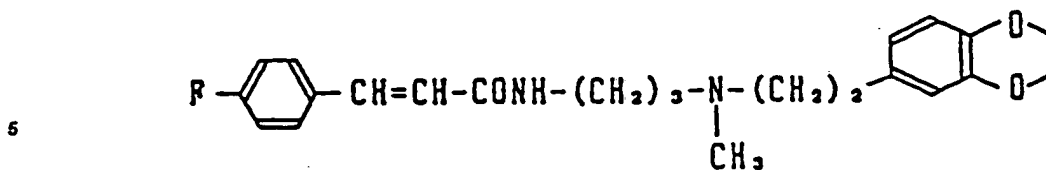
Working Example 112(E)-N-(((3-((N'-(2-(3,4-methylenedioxy)phenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-fluorophenyl)propeneamide

o Yellow oily matter

o NMR(CDCl₃) δ :

1.5 -1.9(2H,m), 2.28(3H,s) 2.4 -2.8(6H,m), 3.3 -3.6(2H,m), 5.81(2H,s), 6.12(1H,d,J=16Hz), 6.69(3H,s), 6.9-7.7(6H,m)

Working Example 113(E)-N-(((3-((N'-(2-(3,4-ethylenedioxy)phenyl)ethyl)-N'-methyl)amino)propyl))-3-(4-fluorophenyl)propeneamide

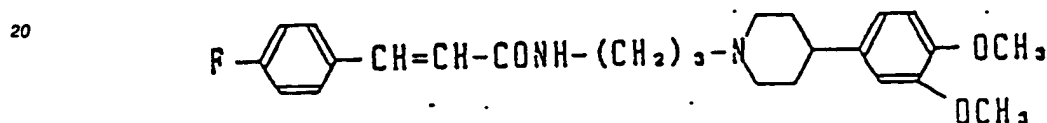


- 10
- o Slightly yellowish oily matter
 - o NMR(CDCl₃) δ ;
1.5 ~1.8(2H,m), 2.28(3H s) 2.4 ~2.8(6H,m), 3.1 ~3.5(2H,m), 4.10(4H,s), 6.00(1H,d,J = 17Hz), 6.4 ~7.8(9H,m)

Working Example 114

15

(E)-N-(((3-((N'-(2-(3,4-dimethoxyphenyl)piperidine-1-yl)propyl)))-3-(4-fluorophenyl)propeneamide



- 25
- o Bright Yellow oily matter
 - o NMR(CDCl₃) δ ;
1.6 ~2.7(11H,m), 3.0 ~3.3(2H,m) 3.3 ~3.6(2H,m), 3.80(3H,s), 3.84(3H,s), 6.28(1H,d,J = 16Hz), 6.69(3H,s), 6.8~7.1(2H,m) 7.1~7.45(3H,m), 7.6(1H,br)

30

Working Example 115

35

(E)-N-(((3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3-benzadipine-3-yl)propyl)-3-(4-fluorophenyl)propeneamide



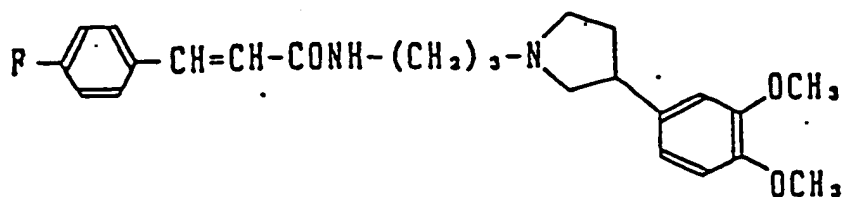
- 45
- o White amorphous matter
 - o NMR(CDCl₃) δ ;
1.6 ~2.0(2H,m), 2.5 ~3.0(10H,m), 3.3 ~3.6(2H,m), 3.83(6H,s), 6.25(1H,d,J = 16Hz), 6.59(2H,s), 6.8 ~7.7(6H,m)

Working Example 116

50

(E)-N-(((3-((3-(3,4-dimethoxyphenyl)pyrrolidine-1-yl)propyl))-3-(4-fluorophenyl)propeneamide

55



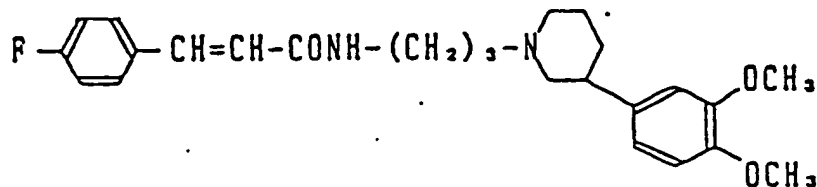
o Bright yellow oily matter

10 o NMR(CDCl₃) δ ;

1.7 -2.6(3H,m), 2.7 -3.7(10H,m), 3.80(3H,s), 3.86(3H,s), 6.40(1H,d,J = 16Hz), 6.7 -7.2(5H,m), 7.3-7.8(3H,m), 7.84(1H,br)

15 Working Example 117

(E)-N-(((3-(3,4-dimethoxyphenyl)piperidine-1-yl)propyl)-3-(4-fluorophenyl)propeneamide



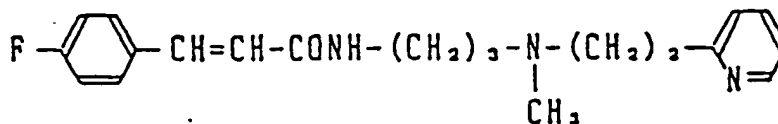
o Bright yellow amorphous matter

o NMR(CDCl₃) δ ;

30 1.2 -2.2(7H,m), 2.5 -2.7(2H,m), 2.9-3.2(2H,m), 3.3-3.6(2H,m), 3.79(6H,s), 6.27(1H,d,J = 16Hz), 6.6-6.8-(3H,m), 6.8 -7.6(6H,m)

Working Example 118

(E)-N-(((3-((2-(2-pyridyl)ethyl)-N'-methyl)amino)propyl)-3-(4-fluorophenyl)propeneamide



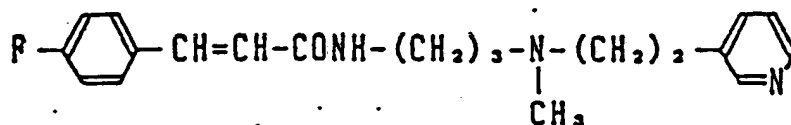
o Yellow oily matter

o NMR(CDCl₃) δ ;

1.5 -1.9(2H,m), 2.24(3H,s), 2.3-3.1(6H,m), 3.2 -3.5(2H,m), 6.24(1H,d,J = 17Hz), 6.9 -7.8(9H,m), 8.4-8.6-(1H,m)

50 Working Example 119

(E)-N-(((3-(N'-(2-(3-pyridyl)ethyl)-N'-methyl)amino)propyl))-3-(4-fluorophenyl)propeneamide



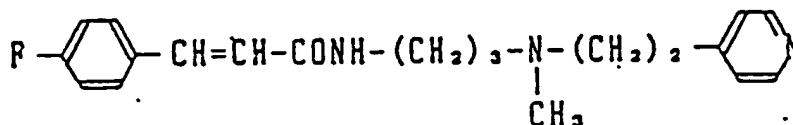
o Yellow oily matter

o NMR(CDCl₃) δ :

10 1.5 -1.9(2H,m), 2.32(3H,s), 2.4-2.9(6H,m), 3.3 -3.6(2H,m), 6.07(1H,d,J = 17Hz), 6.7(1H,br), 6.9-7.4(3H,m),
7.4 -7.7(4H,m), 8.4-8.6(2H,m)

Working Example 120

15 (E)-N-(((3-((N'(2-(4-pyridyl)ethyl)-N'-methyl)amino)propyl))))-3-(4-fluorophenyl)propeneamide



25 o Yellow oily matter

o NMR(CDCl₃) δ :

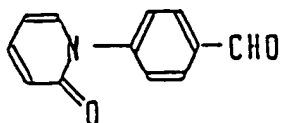
1.5 -1.9(2H,m), 2.32(3H,s), 2.4-2.9(6H,m), 3.3 -3.6(2H,m), 6.09(1H,d,J = 17Hz), 6.65(1H,br), 6.9-7.2(4H,m),
7.3 -7.7(3H,m), 8.4-8.6(2H,m)

30 Examples of the compound III

Preparation Example 1

35

4-(1,2-dihydro-2-oxo-1-pyridyl)benzaldehyde



45 4.4 g of 60 % sodium hydride was suspended into 150 ml of N,N-dimethylformamide, to which 10.78 g of 2-hydroxypyridine was added little by little at a room temperature. 30 min after, 12.4 g of 4-fluorobenzaldehyde was added and stirred at 120 °C for 3 hours. The reaction solution was concentrated under a reduced pressure and iced water was added, which was extracted with chloroform. After drying with anhydrous magnesium sulfate, the solvent was distilled off. Resultant crystals were washed with ethyl
50 acetate to obtain 10.3 g of the above-captioned compound as fine gray powder (yield : 52 %).
Melting point (°C) : 130 - 131

55

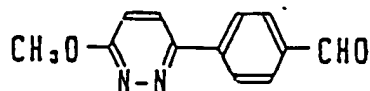
Elemental analysis value : As C ₁₂ H ₉ NO ₂				
		C	H	N
Theoretical value (%)	:	72.35	4.55	7.03
Measured value (%)	:	72.51	4.68	7.12

NMR(CDCl₃) δ :

8.20(1H,dt, J=1.2Hz and 7.2Hz), 8.47(1H,dd, J=1.2Hz and 7.2Hz), 7.1-7.6(4H,m), 7.8-8.0 (2H,m), 10.04-
(1H,s)

Preparation Example 2

4-(3-methoxy-6-pyridaziny)benzaldehyde



Under a nitrogen gas stream, 20 ml of a tetrahydrofuran solution of 12.31 g of 4-bromobenzaldehyde dimethyl acetal was dropped under stirring to a mixture of 1.14 g of magnesium, iodine (catalytic amount) and 30 ml of tetrahydrofuran, to prepare a Grignard reagent. The Grignard reagent thus prepared was dropped under a room temperature to a mixture of 7.00 g of 3-chloro-6-methoxypyridazine, 1.0 g of bis(1,3-diphenylphosphinopropane) nickel (II) chloride and 50 ml of tetrahydrofuran. After stirring at a room temperature for 20 hours, iced water and then 20 ml of 10 % hydrochloric acid were added and stirred for 30 min. Tetrahydrofuran was distilled off under a reduced pressure and the residue was extracted with ethyl acetate. After drying with anhydrous sodium sulfate, the solvent was distilled off and the residue was purified on silica gel column chromatography (solvent : n-hexane - ethyl acetate), to obtain 4.193 g (yield : 48%) of the above-captioned compound as pale orange solid.

Melting point (°C) : 139 - 141

Elemental analysis value : As C ₁₂ H ₁₀ N ₂ O ₃				
		C	H	N
Theoretical value (%)	:	67.28	4.71	13.08
Measured value (%)	:	67.32	4.74	13.24

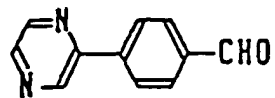
NMR (CDCl₃) δ :

5.18(3H,s), 7.02(1H,d,J=9.4Hz), 7.77 (1H,d,J=9.4Hz), 7.8-8.0(2H,m), 8.0-8.2(2H,m), 10.07(1H,s)

The following compounds were synthesized in the same procedures as in the Preparation Example 2 except for using 2-chloropyridazine, 5-chloro-1-methyl-1,2-dihydro-2-oxopyridine, 3-chloro-6-tert-butylpyridazine, 5-chloro-2-(3,4-dimethoxyphenyl)methylpyridine respectively instead of 3-chloro-6-methoxypyridazine.

4-(2-pyridiny)benzaldehyde

Melting point (°C) : 85.0 - 86.0



5

Melting point ($^{\circ}$ C) : 85.0 - 86.0Elemental analysis value : As $C_{11}H_8N_2O$

10

	C	H	N
Theoretical value (%) :	71.73	4.38	15.21
Measured value (%) :	71.83	4.48	15.17

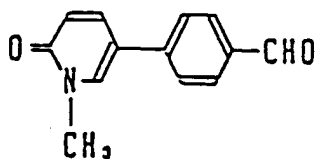
15

NMR ($CDCl_3$) δ :

20 7.9 ~8.2(4H,m), 8.4~8.7(2H,m), 9.00(1H,m), 10.00(1H,s)

4-(1-methyl-1,2-dihydro-2-oxo-5-pyridyl)benzaldehyde

25



30

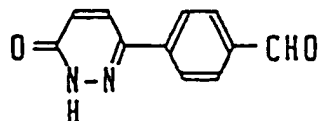
NMR ($CDCl_3$) δ :

35 3.61(3H,s), 6.5 ~6.6(2H,m), 7.5~7.7(4H,m), 7.8 ~7.9(2H,m), 9.92(1H,s)

40

4-(2,3-dihydro-3-oxo-6-pyridazinyl)benzaldehyde

45



50

Melting point ($^{\circ}$ C) : 291 - 292

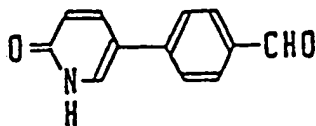
Elemental analysis value : As $C_{11}H_8N_2O_2$				
		C	H	N
Theoretical value (%) :		65.99	4.03	14.00
Measured value (%) :		66.21	4.15	14.02

55

NMR ($CDCl_3$) δ :

7.04(1H,d,J = 10.1Hz), 7.8~8.2(5H,m), 10.06(1H,s), 13.38(1H,br)

4-(1,2-dihydro-2-oxo-5-pyridyl)benzaldehyde



5

Melting point (°C) : 265 - 268.5

10

Elemental analysis value : C ₁₂ H ₉ NO ₂				
		C	H	N
Theoretical value (%)	:	72.35	4.55	7.03
Measured value (%)	:	72.47	4.70	7.02

15

NMR (DMSO-d₆) δ :

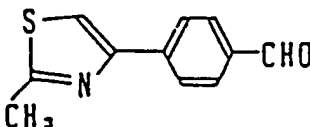
6.4 - 6.6(1H,m), 7.8 - 8.1(6H,m), 10.04(1H,s), 12.0(1H,br)

Preparation Example 3

20

4-(2-methyl-1,3-thiazol-4-yl)benzaldehyde

25



30

2.95 g of 4-(2-methyl-1,3-thiazol-4-yl)benzitrile was dissolved in 100 ml of benzene and thereto was added dropwise a solution in toluene (1.5M) of diisobutylaluminum hydride at the room temperature. Agitation was made for 1 hour. An excess amount of sodium sulfate dihydrate was added to the mixture and the resultant was stirred at the room temperature. A filtrate liquid thereof was concentrated and purified with column chromatography using silica gel and dichloromethane to obtain 1.95 g of the intended compound with a yield of 88%.

35

NMR (CDCl₃) δ : 2.77(3H,s) 7.47(1H,s) 7.8-8.1(4H,m) 10.00(1H,s)

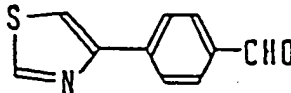
40

Preparation Example 4

4-(1,3-thiazol-4-yl)benzaldehyde

45

(light yellow solid)



50

Production was made in the same as shown in preparation example 3.

NMR (CDCl₃) δ :

55

7.70(1H,d,J = 2Hz)

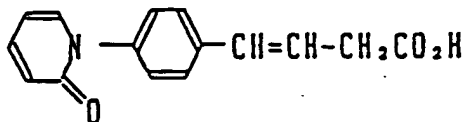
7.8-8.2(4H,m)

8.88(1H,d,J = 2Hz)

10.02(1H,s)

Preparation Example 5

(E)-4-(4-(1,2-dihydro-2-oxo-1-pyridyl)phenyl)-3-butenoic acid



3.00 g of 4-(1,2-dihydro-2-oxo-1-pyridyl)benzaldehyde and 6.15 of β -carboxyethyltriphenyl phosphonium chloride was suspended into 30 ml of tetrahydrofuran, cooled to -50°C and stirred. 20 ml of a tetrahydrofuran solution of 3.72 g of potassium-*tert*-butoxide was dropped and the temperature was gradually raised to 0°C . After 10 hours, iced water was added and the aqueous layer was washed with ether. The aqueous layer was adjusted to about pH 3 with concentrated hydrochloric acid, and deposited crystals were collected by filtration to obtain 2.96g of the above-captioned compound as pale brown yellow powder (yield : 77 %).

Melting point ($^{\circ}\text{C}$) : 218.5 - 221.5

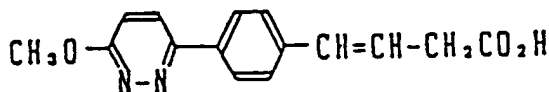
Elemental analysis value : As $\text{C}_{15}\text{H}_{13}\text{NO}_3$				
		C	H	N
Theoretical value (%)	:	70.58	5.13	5.49
Measured value (%)	:	70.55	5.23	5.42

NMR ($\text{DMSO}-d_6$) δ :

3.22(2H,d,J=5.7Hz), 6.1 -6.4(4H,m), 7.1 -7.6(6H,m)

The following compounds were obtained by the same procedures.

(E)-4-(4-(3-methoxy-6-pyridazinyl)phenyl)-3-butenoic acid



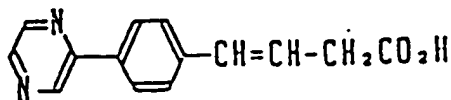
Melting point ($^{\circ}\text{C}$) : 181 - 183

Elemental analysis value : As $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$				
		C	H	N
Theoretical value (%)	:	66.65	5.22	10.37
Measured value (%)	:	66.70	5.08	10.38

NMR ($\text{DMSO}-d_6$) δ :

3.18(2H,d,J=5.7Hz), 4.04(3H,s), 6.28(1H,dt,J=5.7Hz and 15.8Hz), 6.52(1H,d,J=15.8Hz), 7.18-(1H,d,J=9.7Hz), 7.3 -7.6(2H,m), 7.8-8.2(3H,m)

(E)-4-(4-(2-pyridinyl)phenyl)-3-butenoic acid



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Melting point (°C) : 207.0 - 208.5

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Elemental analysis value : As C ₁₄ H ₁₂ NO ₂				
		C	H	N
Theoretical value (%)	:	69.99	5.03	11.66
Measured value (%)	:	69.77	5.09	11.07

15

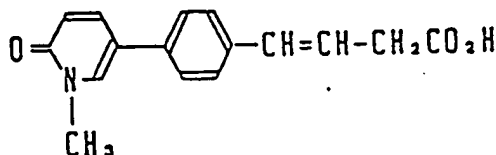
NMR (DMSO-d₆) δ ;

3.25(2H,d,J=6.0Hz), 6.43(1H,dt,J=6.0Hz and 15.5Hz), 8.56(1H,d,J=15.5Hz), 7.60(2H,d,J=8.0Hz), 8.10-(2H,d,J=8.0Hz), 8.59(1H,d,J=3.0Hz), 8.70(1H,dd,J=1.0Hz and 3.0Hz), 9.25(1H,d,J=1.0Hz), 12.4(1H,br s)

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(E)-4-((1-methyl-1,2-dihydro-2-oxo-5-pyridyl)phenyl)-3-butenoic acid

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Melting point (°C) : 217.5 - 219.0 (decomp.)

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Elemental analysis value : As C ₁₆ H ₁₅ NO ₂				
		C	H	N
Theoretical value (%)	:	71.36	5.61	5.20
Measured value (%)	:	71.46	5.65	5.08

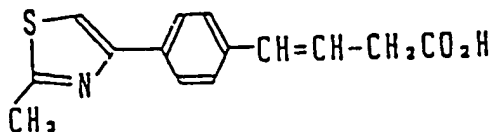
40

NMR (DMSO-d₆) δ ;

3.21(2H,d,J=5.0Hz), 3.51(3H,s), 6.32(1H,dt,J=5.0Hz and 16.0Hz), 6.47 (1H,d,J=9.0Hz), 6.47-(1H,d,J=16.0Hz), 7.4 -7.6(4H,m), 7.82(1H,dd,J=3.0Hz and 9.0Hz), 8.14(1H,d,J=3.0Hz)

(E)-4-((2-methyl-1,3-thiazol-4-yl)phenyl)-3-butenic acid

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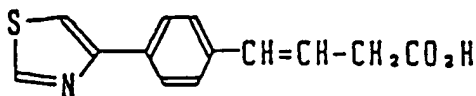
Melting point (°C) : 170 - 171 °C

55

Elemental analysis value : C ₁₄ H ₁₃ NO ₂ S				
	C	H	N	(S)
calcd.	64.84	5.05	5.40	12.36
found	64.88	5.13	5.42	12.33

NMR (CDCl₃ + DMSO-d₆) δ ; 2.73(3H,s) 3.19(2H,d,J = 6Hz), 6.0-6.8(2H,m) 7.2-8.0(5H,m)

(E)-4-(4-(1,3-thiazol-4-yl)phenyl)-3-butenic acid



Melting point (°C) : 190-191 °C

Elemental analysis value : C ₁₃ H ₁₁ NO ₂ S				
	C	H	N	(S)
calcd.	63.65	4.52	5.71	13.07
found	63.45	4.75	5.61	13.20

NMR (CDCl₃ + DMSO-d₆) δ ; 3.20(2H,d,J = 6Hz) 6.1-6.7(2H,m) 7.42(2H,dt,J = 1Hz,8Hz) 7.67(1H,d,J = 2Hz) 7.89(2H,dt,J = 1Hz,8Hz) 8.91(1H,d,J = 2Hz)

(E)-4-(2-(1H-imidazol-1-yl) thiophen-5-yl)-3-butenic acid



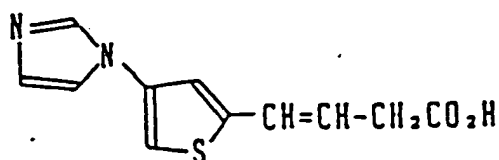
Melting point (°C) : 155.0 - 158.0

Elemental analysis value : As C ₁₁ H ₁₀ N ₂ O ₂ S				
		C	H	N
Theoretical value (%)	:	56.39	4.30	11.98
Measured value (%)	:	56.52	4.22	11.70

NMR (DMSO-d₆) δ ;

3.16(2H,d,J = 7.2Hz), 5.96(1H,dt,J = 7.2Hz and 15.8Hz), 6.50(1H,d,J = 15.8Hz), 6.88(1H,d,J = 3.6Hz), 7.04(1H,s), 7.10 (1H,d,J = 3.6Hz), 7.54(1H,m), 8.04(1H,s)

(E)-4-(4-(1H-imidazol-1-yl) thiophen-2-yl)-3-butenic acid



Melting point (°C) : 177.5 - 179.0

Elemental analysis value : As C₁₁H₁₀N₂O₂S

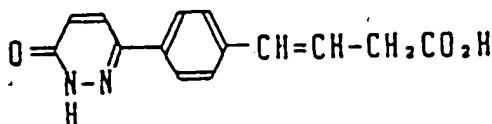
		C	H	N
Theoretical value (%)	:	58.39	4.30	11.98
Measured value (%)	:	58.32	4.30	11.70

NMR (DMSO-d₆) δ :

3.18(2H,d,J=7.6Hz), 6.13(1H,dt,J=7.6Hz and 15.8Hz), 6.56(1H,d,J=15.8Hz), 6.97(1H,s), 7.43(1H,s), 7.49(1H,s), 7.61(1H,s), 8.12(1H,s)

Preparation Example 6

(E)-4-(4-(2,3-dihydro-3-oxo-6-pyridazinyl)phenyl)-3-butenic acid



A mixture of 3.00 g of 4-(2,3-dihydro-3-oxo-6-pyridazinyl) benzaldehyde, 6.12 g of β-ethoxyethyltriphenyl phosphonium chloride and 50 ml of N,N-dimethylformamide was cooled to -50 °C and stirred. 20 ml of an N,N-dimethylformamide solution of 5.55 g of potassium tert-butoxide was dropped and the temperature was gradually raised to 0 °C. After 2 hours, the temperature was elevated to a room temperature and stirring was conducted for further 10 hours. Iced water was added and the aqueous layer was washed with chloroform. The aqueous layer was adjusted to about pH 3 with hydrochloric acid and deposited solids were collected by filtration. They were recrystallized from 50% hydrous N,N-dimethylformamide to obtain 1.51 g of the above-captioned compound as pale orange powder (yield : 39%).

Melting point (°C) : 251 - 254

Elemental analysis value : As C₁₄H₁₂N₂O₂

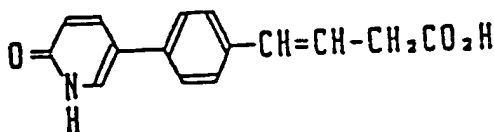
		C	H	N
Theoretical value (%)	:	65.61	4.72	10.93
Measured value (%)	:	65.78	4.70	10.91

NMR (DMSO-d₆) δ :

3.23(2H,d,J=5.7Hz), 6.37(1H,dt,J=5.7 Hz and 15.8Hz), 6.59(1H,d,J=15.8Hz), 6.98(1H,d,J=10.1Hz), 7.51(2H,d,J=8.4Hz), 7.83(2H,d,J=8.4Hz), 8.03(1H,d,J=10.1Hz), 13.15(1H,br)

The following compounds were synthesized in the same procedures.

(E)-4-(4-(1,2-dihydro-2-oxo-5-pyridyl)phenyl)-3-butenic acid



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Melting point (°C) : 250 (decomposed)

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Elemental analysis value C ₁₅ H ₁₃ NO ₃			
	C	H	N
calcd. (%)	70.58	5.13	5.49
found .(%)	70.67	5.21	5.29

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NMR (DMSO-d₆) δ :

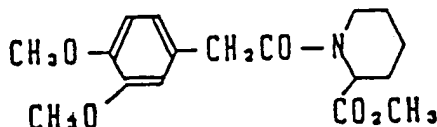
3.20(2H,d,J = 6Hz), 6.1-6.6(3H,m), 7.2-7.6(4H,m) 7.6-7.9(2H,m), 12.0(1H.br)

Preparation Example 7

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Methyl N-(3,4-dimethoxyphenylacetyl)piperidine-2-carboxylate

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5.00 g of piperidine-2-carboxylic acid was dissolved into an aqueous 80 ml solution of saturated sodium hydrogen carbonate and stirred at a room temperature. 20 ml of an acetonitrile solution of 9.2 g of 3,4-dimethoxyphenyl acetyl chloride was dropped and stirred for 30 min. After washing the aqueous layer with ethyl acetate, the aqueous layer was adjusted to about pH 2 with concentrated hydrochloric acid and extracted with chloroform. Chloroform was distilled off and the resultant residue was refluxed for 6 hours with addition of 150 ml of methanol and 0.5 ml of concentrated sulfuric acid. After distilling off methanol, an aqueous diluted solution of sodium hydrogen carbonate was added and extracted with ethyl acetate. After drying with anhydrous magnesium sulfate, the solvent was distilled off and the residue was purified on silica gel column chromatography (solvent : n-hexane : ethyl acetate = 1:1) to obtain 3.94 of the above-captioned compound as yellow oil (yield : 32%).

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NMR (CDCl₃) δ :

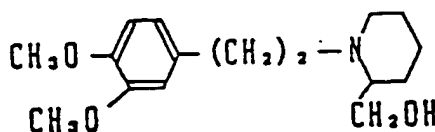
1.1 ~1.9(5H,m), 2.0-2.2(1H,m), 2.9-3.3(1H,m), 3.56(1H,d,J = 14Hz), 3.68(3H,s), 3.78(1H,d,J = 14Hz), 3.82-(3H,s), 3.84(3H,s), 4.4 ~4.7(1H,m), 5.40(1H,m), 7.76(3H,s)

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Preparation Example 8

N-(2-(3,4-dimethoxyphenyl)ethyl)piperidine-2-methanol

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2.33 g of lithium aluminum hydride was suspended into 50 ml of tetrahydrofuran and stirred. 3.94 g of

methyl N-(3,4-dimethoxyphenylacetyl)piperidine-2-carboxylate was dissolved in 20 ml of tetrahydrofuran, which was dropped and, thereafter, refluxed for 30 min. After cooling with ice and decomposing the excess reagent with ethyl acetate, 2.3 ml of water, 2.3 ml of an aqueous 15% solution of sodium hydroxide and 7 ml of water were added successively and, further, anhydrous magnesium sulfate was added and stirred.

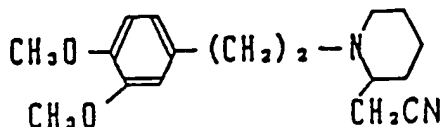
Insoluble matters were filtered out and the filtrate was washed thoroughly with tetrahydrofuran. The filtrate was concentrated and purified on silica gel column chromatography (solvent : dichloromethane : methanol : concentrated aqueous ammonium = 1000 : 100 : 2), to obtain 2.77 g of the above-captioned compound as white solid (yield : 81 %).

NMR (CDCl₃) δ ;

1.1 -1.8(6H,m), 2.2-3.2(8H,m), 3.44(1H,dd,J=5Hz and 12Hz), 3.68(1H,dd,J=4Hz and 12Hz), 3.81(3H,s), 3.84(3H,s), 6.5 -6.8(3H,m)

Preparation Example 9

N-2-(3,4-dimethoxyphenyl)ethyl)piperidine-1-acetonitrile



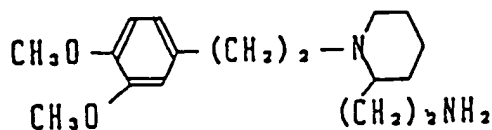
2.77 g of N-2-(3,4-dimethoxyphenyl)ethyl)piperidine-2-methanol was dissolved in 30 ml of chloroform and cooled with ice. 0.87 ml of thionyl chloride was dropped and stirred at a room temperature for 48 hours. An aqueous solution of saturated sodium hydrogen carbonate was added and extracted with chloroform. After drying with anhydrous sodium sulfate, the solvent was distilled off and the residue was purified on silica gel column chromatography (solvent : dichloromethane : methanol = 100 : 1) can be obtained 2.77 g of pale yellow oil. 1.21 g of potassium cyanate, dicyclohexyl-18-crown-6 (catalytic amount) and 20 ml of acetonitrile were added and refluxed for 24 hours. After allowing them to cool, an aqueous solution of potassium carbonate was added and extracted with ethyl acetate. After washing with water and drying with anhydrous sodium sulfate, the solvent was distilled off. The residue was purified on silica gel column chromatography (solvent : n-hexane : ethyl acetate = 2:1), to obtain 920 mg of the above-captioned compound as yellow oil (yield : 34%).

NMR (CDCl₃) δ ;

1.3 -1.8(6H,m), 2.3-2.9(9H,m), 3.84(3H,s), 3.86(3H,s), 6.8 -6.9(3H,m)

Preparation Example 10

N-2-(3,4-dimethoxyphenyl)ethyl)-2-(2-aminoethyl)piperidine



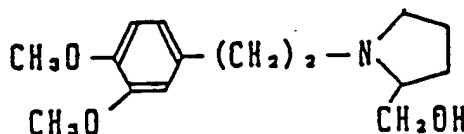
10 ml of a tetrahydrofuran solution of 920 mg of N-2-(3,4-dimethoxyphenyl)ethyl)piperidine-2-acetonitrile was dropped at a room temperature to a mixture of 360 mg of aluminum lithium hydride and 10 ml of tetrahydrofuran. After stirring for 18 hours, it was cooled with ice, to which sodium sulfate-10 hydrate was added little by little and stirred violently for 30 min. The insoluble matters were filtered out and the filtrate was washed thoroughly with tetrahydrofuran. The filtrate was concentrated and purified on silica gel column chromatography (solvent: dichloromethane : methanol : concentrated aqueous ammonium = 200 : 20 : 1), to obtain 650 mg of the above-captioned compound as pale yellow oil (yield : 70%)

NMR (CDCl₃) δ :

1.1 -2.0(8H,m), 2.0-3.1(10H,m), 3.5 -3.7(1H,m), 3.84(3H,s), 3.87(3H,s), 6.6 -6.9(3H,m)

Preparation Example 11

(S)-N-2-(3,4-dimethoxyphenyl)ethylpyrrolidine-2-methanol



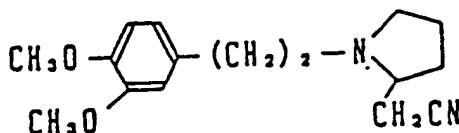
50 ml of acetonitrile was added to 1.0 g of S-(+)-prolinole, 1.9 g of 2-(3,4-dimethoxyphenyl)ethyl-chloride and 1.64 g of anhydrous potassium carbonate and refluxed under heating for one day. After distilling off the solvent under a reduced pressure, about 50 ml of methylene chloride was added and deposited inorganic salts were filtered out. After distilling off methylene chloride under a reduced pressure, the residue was purified on silica gel column chromatography, to obtain 0.83 g of the above-captioned compound (yield : 32 %).

NMR (CDCl₃) δ :

1.7 -2.0(4H,m), 2.3-3.4(7H,m), 3.47(1H,dd,J=4.0Hz and 11.0Hz), 3.66(1H,dd, J=4.0Hz and 11.0Hz), 3.88-(3H,s), 3.91(3H,s), 4.38(1H,br s), 6.7-6.9(3H,m)

Preparation Example 12

(S)-N-2-(3,4-dimethoxyphenyl)ethylpyrrolidine-2-acetonitrile



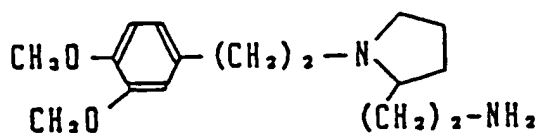
The above-captioned compound was obtained by the same procedures as those in Preparation Example 9 except for using (S)-N-2-(3,4-dimethoxyphenyl)ethylpyrrolidine-2-methanol as the starting material.

NMR (CDCl₃) δ :

1.5 -3.1(12H,m), 3.1-3.3(1H,m), 3.81(3H,s), 3.84(3H,s), 6.6 -6.8(3H,m)

Preparation Example 13

(S)-N-2-(3,4-dimethoxyphenyl)ethyl-2-(2-aminoethyl) pyrrolidine



The above-captioned compound was obtained by the same procedures as those in Preparation Example 10 except for using (S)-N-(2-(3,4-dimethoxyphenyl)ethyl)pyrrolidine-2-acetonitrile as the starting material.

NMR (CDCl₃) δ :

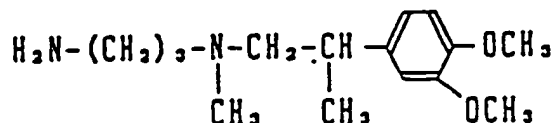
1.1 -3.3(16H,m), 3.5 -3.8(1H,m), 3.82(3H,s), 3.84(3H,s), 6.6 -6.9(3H,m)

Preparation Example 14

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N-methyl-N-2-(3,4-dimethoxyphenyl)propyl)-1,3-propane diamine

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A mixture of 1.55 g of N-methyl-N-2-(3,4-dimethoxyphenyl)propyl)amine, 1.98 g of N-(3-bromopropyl)phthalimide, 1.0 g of anhydrous potassium carbonate and 10 ml of acetonitrile was refluxed under heating for 8 hours. They were allowed to cool and then concentrated after filtering out insoluble matters. The residue was purified on silica gel column chromatography (solvent : chloroform : methanol = 100 : 1), to obtain 2.71 g of N-(3-(N'-2-(3,4-dimethoxyphenyl)propyl)-N'-methylamino)propyl)phthalimide as yellow oil.

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The product was dissolved in 20 ml of ethanol, to which 0.4 ml of hydrazine monohydrate was added and refluxed under heating for 2 hours. Deposited matters were filtered out and diluted aqueous solution of sodium hydroxide was added, which was extracted with chloroform. After drying with anhydrous sodium sulfate, the solvent was distilled off and the residue was purified on silica gel column chromatography (solvent : chloroform : methanol : concentrated aqueous ammonia : 100 : 10 : 1) to obtain 1.54 g of the above-captioned compound as yellow oil (yield :78 %).

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NMR (CDCl₃) δ :

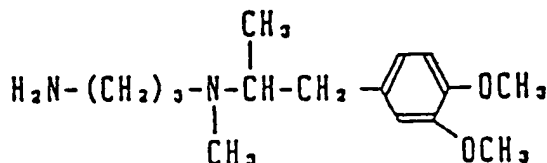
1.23(3H,d,J=6.6Hz), 1.3 -1.7(12H,m), 2.20(3H,s), 2.2 -2.5(4H,m), 2.5-3.1(3H,m), 3.84(3H,s), 3.87(3H,s), 6.5 -6.8(3H,m)

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Preparation Example 15

N-methyl-N-(3-(3,4-dimethoxyphenyl)propan-2-yl)-1,3-propane diamine

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The above-captioned compound was obtained in the same procedures as those in preparation Example 13 by using N-methyl-N-(3-(3,4-dimethoxyphenyl)propan-2-yl)amine instead of N-methyl-N-2-(3,4-dimethoxyphenyl)propyl)amine.

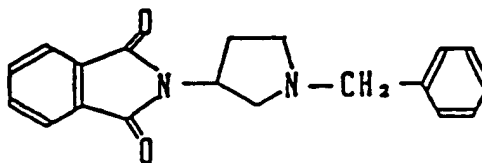
Yellow oil NMR (CDCl₃) δ :

0.92(3H,d,J=6.6Hz), 1.3 -1.8(4H,m), 2.1 -3.1(10H,m), 3.84(3H,s), 3.86(3H,s), 6.6 -6.9(3H,m)

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Preparation Example 16

N-(1-benzylpyrrolidin-3-yl)phthalimide

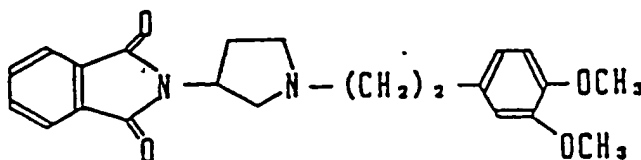


10.0 g of 3-amino-1-benzylpyrrolidine was dissolved into 10 ml of chloromethane, to which 12.4 g of N-ethoxy-carbonylphthalimide was added and stirred at a room temperature for 10 hours. The solvent was distilled off, diethyl ether was added and insoluble matters were filtered out. The filtrate was concentrated and purified on silica gel column chromatography, to obtain 12.70 g of the above-captioned compound (yield : 73 %)

NMR (CDCl₃) δ ;
2.1 ~2.3(2H,m), 2.6~3.1(4H,m), 3.86(2H,s), 4.7 ~5.1(1H,m), 7.1~7.3(5H,m), 7.6 ~7.8(4H,m)

Preparation Example 17

N-(1-(2-(3,4-dimethoxyphenyl)ethyl)pyrrolidin-3-yl)phthalimide



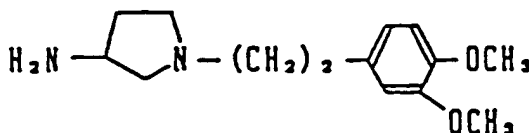
12.70 g of N-(1-benzylpyrrolidin-3-yl)phthalimide was dissolved in 100 ml of ethanol and then subjected to hydrogenating decomposition with addition of 1.0 g of 10 % palladium-carbon and 5.2 ml of concentrated hydrochloric acid at 60 °C under 1 atm. After 12 hours, the catalyst was filtered out and the solvent was distilled off to obtain 11.03 g of N-(3-pyrrolidyl)phthalimide hydrochloride.

6.03 g of the hydrochloride was suspended into 100 ml of acetonitrile, to which 4.79 g of 2-(3,4-dimethoxyphenyl) ethyl chloride, 8.24 g of anhydrous potassium carbonate and n-tetrabutyl ammonium iodide (catalytic amount) were added and refluxed under heating for 20 hours. After allowing them to cool, the inorganic salts were filtered out and the solvent was distilled off. After adding ethyl acetate and washed with water, they were dried with anhydrous magnesium sulfate. The solvent was concentrated and purified on silica gel chromatography to obtain 1.03 g of the above-captioned compound (total yield : 6.5 %).

NMR (CDCl₃) δ ;
2.1 ~2.5(2H,m), 2.6~3.2(8H,m), 3.87 (3H,s), 3.90(3H,s), 4.95(1H,m), 6.80 (3H,bs), 7.6 ~7.9(4H,m)

Preparation Example 18

3-amino-1-(2-(3,4-dimethoxyphenyl)ethyl)pyrrolidine



1.03 g of N-(1-(2-(3,4-dimethoxyphenyl)ethyl)pyrrolidin-3-yl)phthalimide was dissolved in 50 ml of ethanol, to which 2 ml of hydrazine monohydrate was added and refluxed under heating for 14 hours. The solvent was distilled off and an aqueous diluted solution of sodium hydroxide was added to the residue and extracted with chloroform. After drying with anhydrous magnesium sulfate, the solvent was distilled off, to obtain 0.88 g of the above-captioned compound (yield : 100 %).

NMR (CDCl₃) δ ;

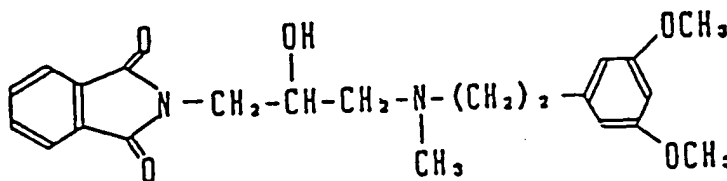
1.4 -1.7(3H,m), 2.1-2.9(9H,m), 3.4 -3.6(1H,m), 3.86(3H,s), 3.88(3H,s), 6.7 -6.9(3H,m)

10 Preparation Example 19

N-(3-((N'-(2-(3,5-dimethoxyphenyl)ethyl)-N'-methyl)amino)-2-hydroxypropyl)phthalimide

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1.25 g of N-(2,3-epoxypropyl)phthalimide and 1.0 g of N-methyl-2-(3,5-dimethoxyphenyl)ethylamine were dissolved in 50 ml of ethanol and stirred at 40 °C for 12 hours. After distilling off the solvent, the residue was purified on silica gel column chromatography, to obtain 1.90 g of the above-captioned compound as yellow oil (yield : 93%).

NMR (CDCl₃) δ ;

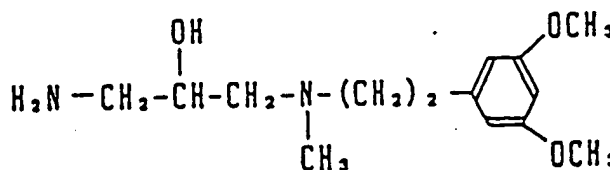
2.32(3H,s), 2.46(2H,d,J = 6.0Hz), 2.6-2.8(4H,m), 3.4(1H,brs), 3.8-4.1(9H,m), 6.2-6.4(3H,m) 7.6-7.9(4H,m)

30

Preparation Example 20

35 N-methyl-N-(2-(3,5-dimethoxyphenyl)ethyl)-2-hydroxy-1,3-propane diamine

40



45

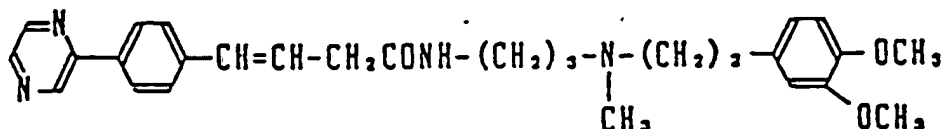
Using N-(3-((N'-(2-(3,5-dimethoxyphenyl)ethyl)-N'-methyl)amino)-2-hydroxypropyl)phthalimide at the starting material, a crude product was obtained in the same procedures as those in Preparation Example 18. Purification was effected by silica gel column chromatography (solvent : dichloromethane : methanol : concentrated aqueous ammonia), to obtain the above-captioned compound.

50 NMR (CDCl₃) δ ;

2.15(3H,br s, exchangeable with D₂O), 2.3 -2.5(5H,m), 2.5-3.0(6H,m), 3.4-3.7(1H,m), 3.76(6H,s), 6.32(3H,br s)

55 Example 1

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(pyridinyl)phenyl)-3-buteneamide



5

1.03 g of (E)-4-(4-(2-pyridinyl)phenyl)-3-butenic acid, 0.90 g of N,N'-dicyclohexylcarbodiimide, 0.59 g of N-hydroxybenzotriazole, 1.16 g of N-2-((3,4-dimethoxyphenyl)ethyl)-N-methyl-1,3-propane diamine and a mixture of 10 ml acetonitrile and 10 ml of water were stirred at 60 °C for 30 min. Deposited crystals were filtered out and the solution was concentrated under a reduced pressure. Purification was effected by silica gel column chromatography, to obtain 1.03 g of the above-captioned compound as pale yellow crystal. Melting point (°C) : 84.5-86.0

15

Elemental analysis value : As C ₂₈ H ₃₄ N ₄ O ₃				
		C	H	N
Theoretical value (%)	:	70.86	7.22	11.81
Measured value (%)	:	70.84	7.24	11.83

20

NMR (CDCl₃) δ ;

1.5 -1.9(2H,m), 2.20(3H,s), 2.2-2.7(6H,m), 3.04(2H,d,J=6.0Hz), 3.2 -3.5(2H,m), 3.80(6H,s), 6.28-(1H,dt,J=6.0Hz, and 17.0Hz), 6.40(1H,d,J=17.0Hz), 6.5 -6.7(3H,m), 7.18(1H,br s), 7.3 -7.4(2H,m), 7.8 -7.9-(2H,m), 8.3-8.5(2H,m), 8.88(1H,br s)

25

Examples 2 - 18

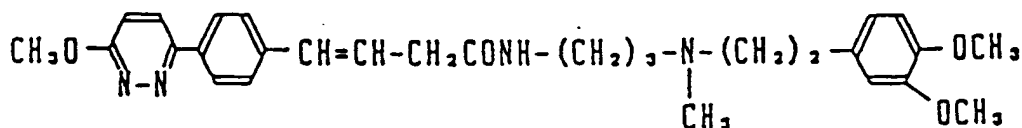
The following compounds were synthesized in the same procedures as those in Example 1.

Example 2

35

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(3-methoxy-6-pyridazinyl)phenyl)-3-butenic acid

40



45

Melting point (°C) : 116-118

50

Elemental analysis value : As C ₂₉ H ₃₅ N ₄ O ₄				
		C	H	N
Theoretical value (%)	:	69.02	7.19	11.10
Measured value (%)	:	69.06	7.17	11.04

55

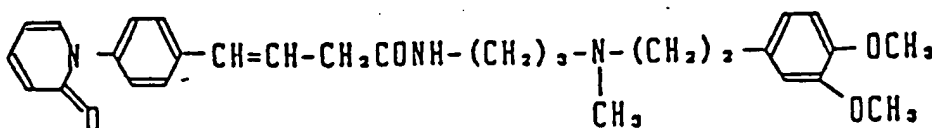
NMR (CDCl₃) δ ;

1.5 -1.9(2H,m), 2.3-2.8(6H,m), 3.08(2H,d,J=6.2Hz), 3.2 -3.5(2H,m), 3.82(6H,s), 4.18(3H,s), 6.22-(1H,dt,J=6.2Hz and 15.1Hz), 6.52(1H,d,J=15.1Hz), 6.6 -6.8(3H,m), 7.02(1H,d,J=9.2Hz) 7.27(1H,br), 7.44-

(1H,d,J=8.4Hz), 7.73(1H,d, J=9.2Hz), 7.93(1H,d,J=8.4Hz)

Example 3

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(1,2-dihydro-2-oxo-1-pyridyl)-phenyl)-3-buteneamide



Melting point (°C) : 114-116

Elemental analysis value : As C₂₉H₃₅N₃O₄·1/4 H₂O

		C	H	N
Theoretical value (%)	:	70.49	7.24	8.50
Measured value (%)	:	70.20	7.07	8.42

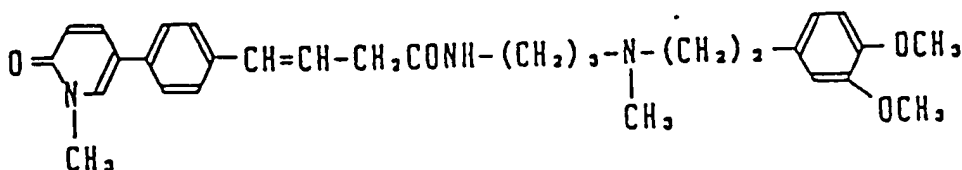
NMR (CDCl₃) δ :

1.5 -1.9(2H,m), 2.16(3H,s), 2.4-2.9(6H,m), 3.06(2H,d,J=6.2Hz), 3.1 -3.5(2H,m), 3.80(3H,s), 3.82(3H,s), 5.9 -6.8(7H,m), 6.9-7.5(7H,m)

Example 4

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(1-methyl-1,2-dihydro-2-oxo-5-pyridyl)phenyl)-3-buteneamide

(Yellow oil)



NMR (CDCl₃) δ :

1.5 -1.9(2H,m), 2.23(3H,s), 2.4-2.7(6H,m), 3.06(2H,d, J=6Hz), 3.2-3.5(2H,m), 3.60(3H,s), 3.82(3H,s) 3.83-(3H,s) 6.26(1H,dt,J=6Hz and 16Hz), 6.43(1H,d,J=16Hz), 6.5-6.8(4H,m), 7.2-7.4(5H,m), 7.46(1H,d,J=3Hz), 7.58(1H,dd,J=3Hz, 9Hz)

Example 5

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl)amino)propyl)-4-(4-(1,2-dihydro-2-oxo-5-pyridyl)-phenyl)-3-buteneamide

(Yellow solid)



NMR (CDCl₃) δ ;
 1.5 ~1.8(2H,m), 2.20(3H,s), 2.4~2.8(6H,m), 3.04(2H,d, J=7Hz), 3.2~3.5(2H,m), 3.72(3H,s), 3.80(3H,s) 6.1~6.5-
 10 (2H,m), 6.5~6.8(4H,m), 7.2~7.8(7H,m)

Example 6

15 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(2,3-dihydro-3-oxo-6-pyridazinyl)-phenyl)-3-buteneamide



25 Melting point (°C) : 129 - 131

30

Elemental analysis value : As C ₂₈ H ₃₄ N ₄ O ₄ ·1/4 H ₂ O				
		C	H	N
Theoretical value (%)	:	67.92	7.02	11.32
Measured value (%)	:	67.86	6.97	11.35

NMR (CDCl₃) δ ;
 35 1.5 ~1.9(2H,m), 2.21(3H,s), 2.3~2.8(6H,m), 3.07(2H,d,J=5.7Hz), 3.2~3.5(2H,m), 3.82(3H,s), 3.83(3H,s) 6.0
 ~6.9(5H,m), 7.03(1H,d,J=9.7Hz), 7.2~7.5(3H,m), 7.5 ~7.8(3H,m)

Example 7

40 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1,3-thiazol-4-yl)phenyl)-3-buteneamide

(light yellow oil)



NMR (CDCl₃) δ ;
 55 1.4~1.9(2H,m), 2.14(3H,s), 2.3~2.7(6H,m) 3.04(2H,d,J=6Hz), 3.1~3.5(2H,m), 3.78(6H,s) 5.9~6.8 (5H,m), 7.40-
 (1H,brs), 7.44(1H,d,J=2Hz), 7.5~8.0(4H,m), 8.77(1H,d,J=2Hz)

Example 8

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(2-methyl-1,3-thiazol-4-yl)phenyl)-3-butene amide

(light yellow oil)

5

10



NMR (CDCl₃) δ :

1.4-1.9(2H,m), 2.15(3H,s), 2.3-2.9(9H,m) 3.05(2H,d,J=6Hz), 3.1-3.5(2H,m) 3.81(6H,s), 6.1-6.8 (5H,m), 7.1-8.0(6H,m)

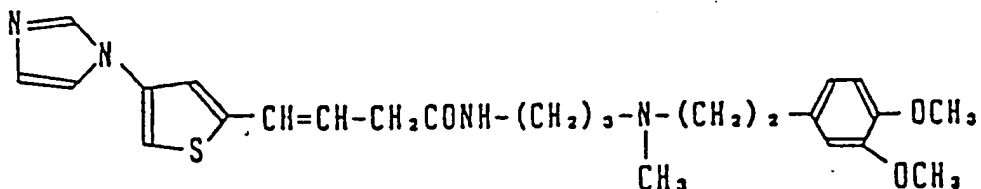
15

Example 9

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-imidazol-1-yl)thiophen-2-yl)-3-butene amide

25

30



Yellow oil

NMR (CDCl₃) δ :

1.5 -1.9(2H,m), 2.24(3H,s), 2.4-2.8(6H,m), 2.97(2H,d,J=6.5Hz), 3.1 -3.5(2H,m), 3.78(3H,s), 3.81(3H,s), 6.08 (1H,dt,J=6.5Hz and 15.5Hz) 6.46(1H,d,J=15.5Hz), 6.6-6.8(3H,m), 6.91(2H,s), 7.0 -7.2(2H,m), 7.30(1H,br), 7.68(1H,s)

35

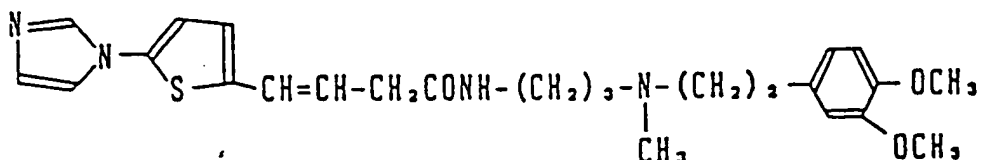
Example 10

40

(E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(2-(1H-imidazol-1-yl)thiophen-5-yl)-3-butene amide

45

50



Yellow oil

NMR (CDCl₃) δ :

1.5 -1.9(2H,m), 2.13(3H,s), 2.4-2.8(6H,m), 2.96(1H,d,J=6.5Hz), 3.2 -3.5(2H,m), 3.80(3H,s), 3.82(3H,s) 5.97 (1H,dt,J=6.5Hz and 15.8Hz) 6.42(1H,d,J=15.8Hz), 6.6-6.9(5H,m), 7.08(2H,s), 7.28(1H,br), 7.64(1H,s)

55

Example 11

(E)-N-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-3-pyrrolidino)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butene amide

5



Yellow oil

15 NMR (CDCl₃) δ ;

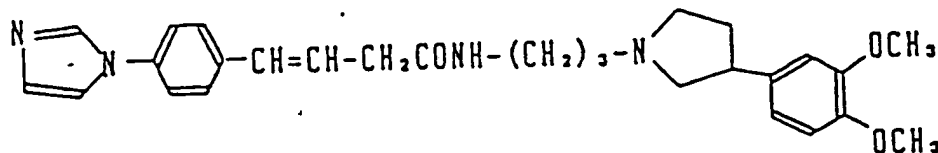
1.5 -1.9(1H,m), 2.1-3.0(9H,m), 3.12(2H,d,J = 6.5Hz), 3.78(3H,s), 3.80(3H,s), 6.34(1H,dt,J = 6.5Hz and 17.0Hz)
6.44 (1H,d,J = 17.0Hz), 6.6-6.8(4H,m), 7.11 (1H,br s), 7.2-7.5(5H,m), 7.77(1H,br s)

Example 12

20

(E)-N-(3-(3-(3,4-dimethoxyphenyl)-1-pyrrolidino)propyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butene amide

25



Yellow oil

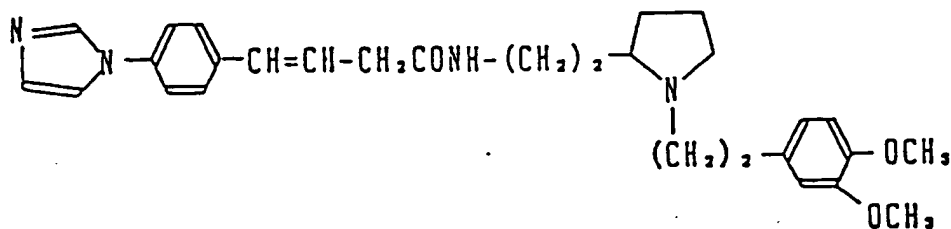
NMR (CDCl₃-CD₃OD) δ ;

1.7 -2.0(2H,m), 2.0-2.4(1H,m), 2.5-3.5(12H,m), 3.83(3H,s), 3.86(3H,s), 6.40(1H,dt,J = 6.5Hz and 16.2Hz)
35 6.48(1H,d,J = 16.2Hz), 6.7-6.9(3H,m), 7.2-7.5(6H,m), 7.81(1H,m)

Example 13

40 (E)-N-(2-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-2-pyrrolidino)ethyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butene amide

45



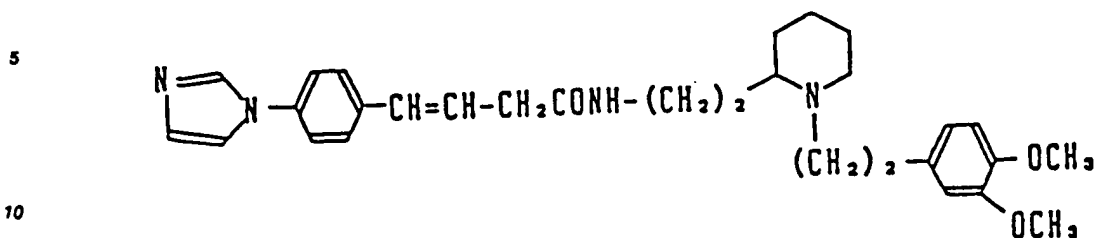
Yellow oil

NMR (CDCl₃) δ ;

1.5 -3.5(17H,m), 3.80(3H,s), 3.82(3H, s), 6.28(1H,dt,J = 6.5Hz and 16.0Hz), 6.40(1H,d,J = 16.0Hz), 6.5-6.8-
55 (3H,m), 7.1-7.4(7H,m), 7.75(1H,br s)

Example 14

(E)-N-(2-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-2-piperidino)ethyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butene amide



Yellow oil

NMR (CDCl₃) δ :

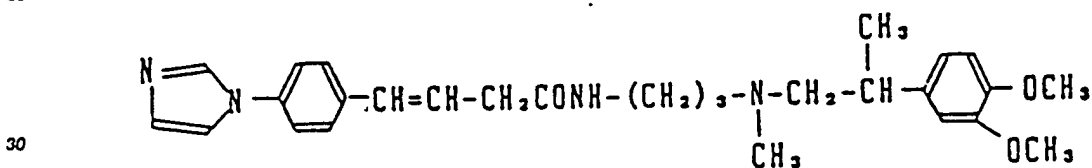
15 1.2-2.0(8H,m), 2.3-3.6(10H,m), 3.81 (3H,s), 3.84(3H,s), 3.9-4.5(1H,m), 6.24(1H,dt,J=6Hz and 16Hz), 6.45-
(1H,d,J=16Hz), 6.5-6.8(3H,m), 7.0-7.5(7H,m), 7.80(1H,s)

Example 15

20

(E)-N-(3-(N'-(2-(3,4-dimethoxyphenyl)propyl)-N'-methyl) amino)propyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butene amide

25



Yellow oil

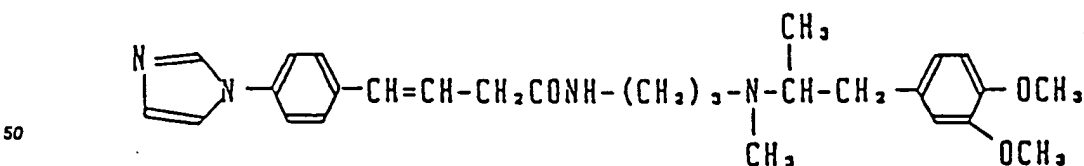
NMR (CDCl₃) δ :

35 1.20(3H,d,J=6.8Hz), 1.4-1.8(2H,m), 2.13(3H,s), 2.3-2.6(4H,m), 2.6-3.0(3H,m), 3.1-3.4(2H,m), 3.79(3H,s),
3.84(3H,s) 6.13(1H,dt,J=5.8Hz and 15.1Hz), 6.37(1H,d,J=15.1Hz), 6.5-6.8(3H,m), 6.90(1H,br), 7.1-7.5-
(6H,m), 7.76(1H,s)

40 Example 16

(E)-N-(3-(N'-(3-(3,4-dimethoxyphenyl)-2-propyl)-N'-methylpropyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butene amide

45



Yellow oil

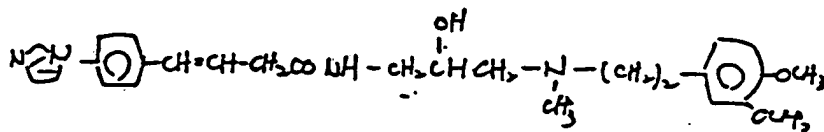
NMR (CDCl₃) δ :

55 0.92(3H,d,J=6.5Hz), 1.5-1.9(2H,m), 2.23(3H,s), 2.3-3.1(5H,m), 3.3-3.5(2H,m), 3.82(3H,s), 3.84(3H,s), 6.25
(1H,dt,J=6.2Hz and 15.8Hz), 6.50(1H,d,J=15.8Hz), 6.6-6.9(3H,m), 7.1-7.6(7H,m), 7.83(1H,s)

Example 17

(E)-N-(3-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methyl) amino)-2-hydroxypropyl)-4-(4-(1H-imidazol-1-yl)-phenyl)-3-buteneamide

(light yellow, viscous liquid)

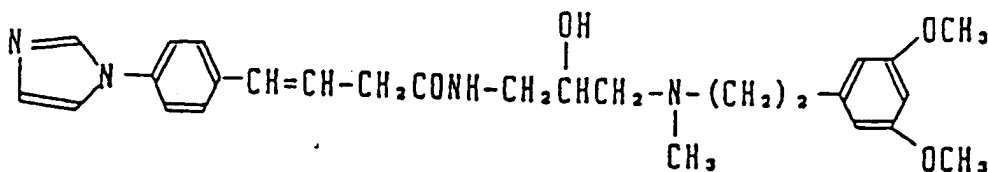


NMR (CDCl₃) δ ; 2.32(3H,s), 2.4(2H,d,J = 7Hz), 2.5-2.8(4H,m), 2.9-3.5(4H,m), 3.16(2H,d,J = 7Hz), 3.8(3H,s), 3.84 (3H,s), 6.0-6.5(2H,m), 6.5-6.8(3H,m), 7.1-7.5(7H,m), 7.8(1H,s).

Example 18

(E)-N-(3-(N'-(2-(3,5-dimethoxyphenyl)ethyl)-N'-methyl) amino)-2-hydroxypropyl)-4-(4-(1H-imidazol-1-yl)-phenyl)-3-butene amide

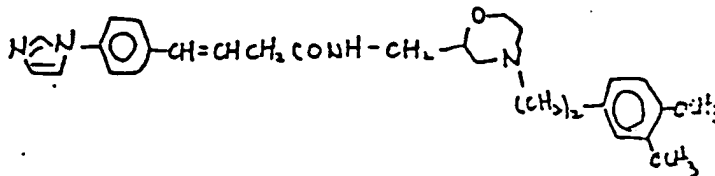
(colorless oil)



NMR (CDCl₃) δ ; 2.32(3H,s) 2.39(2H,d,J = 7.0Hz) 2.5-2.8(4H,m) 3.0-3.8(12H,m) 6.1-6.4 (4H,m) 6.50- (1H,d,J = 16.0Hz) 7.1-7.5(6H,m) 7.83(1H,brs)

Example 19

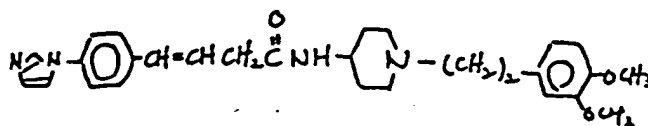
(E)-N-(3-(1-(2-(3,4-dimethoxyphenyl)-3-morpholino)-methyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-buteneamide



NMR (CDCl₃) δ ; 1.8-2.2(2H,m) 2.2-3.0(6H,m) 3.0-3.4(3H,m) 3.4-4.1(10H,m) 6.16(1H,brs) 6.32- (1H,dt,J = 6.1Hz, 15.5Hz) 6.48(1H,d,J = 15.5Hz) 6.7-6.8(3H,m) 7.14(1H,brs) 7.2-7.5(5H,m) 7.80(1H,brs)

Example 20

(E)-N-(1-(2-(3,4-dimethoxyphenyl)ethyl)-4-piperidino)-4-(4-(1H-imidazol-1-yl)phenyl)-3-buteneamide



5

mp 161-161.5° C

10

C ₂₈ H ₂₄ N ₄ O ₃			
	C	H	N
calcd.	70.86	7.22	11.81
found	70.98	7.33	11.80

15

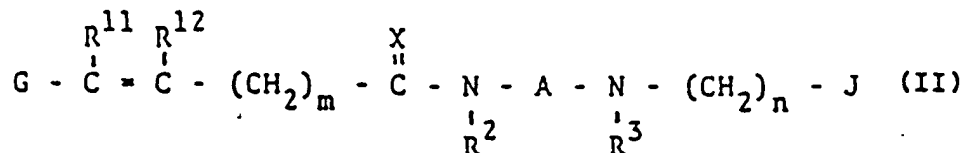
NMR (CDCl₃) δ ; 1.1-1.7(2H,m) 1.8-2.3(4H,m) 2.4-3.0(6H,m) 3.14(2H,d,J=6.5Hz) 3.75(1H,m) 3.86(3H,s), 3.88(3H,s) 5.84(1H,brd,J=7Hz) 6.29(1H,dt,J=6.5Hz, 15.1Hz) 6.53(1H,d,J=15.1Hz) 6.8-6.8(3H,m) 7.1-7.6-(6H,m) 7.81(1H,s)

20

Claims

1. A butenoic or propeonic acid derivative having the formula (II) and a pharmacologically acceptable salt thereof:

25



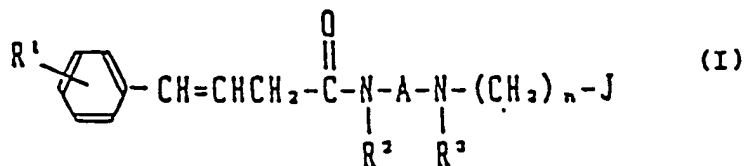
30

which is defined by each of the following definitions (I), (II) and (III):

(I) having the formula (I) in which in the formula

35

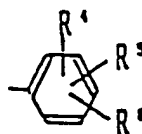
(II) G is R¹-phenyl, R¹¹ and R¹² each are hydrogen, m is one and X is oxygen,



40

wherein R¹ is a hetero-aryl group, R² and R³ each are hydrogen, a lower alkyl, a cycloalkyl or an allyl group, or R² and R³ may form a 5- to 7-membered saturated heterocyclic ring together with the nitrogen atom to which they are bonded, A is an alkylene group having 1 to 6 carbon atoms, which alkylene may have a lower alkyl, a lower alkoxy or hydroxy, J is pyridyl or a phenyl having substituents R⁴, R⁵ and R⁶:

50



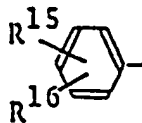
55

which R⁴, R⁵ and R⁶ each are hydrogen, a halogen atom, a lower alkyl, a lower alkoxy, hydroxy, nitro, cyano, trifluoromethyl, an alkylsulfonyloxy, -NR⁷R⁸, R⁷ and R⁸ being hydrogen or a lower alkyl, or an

alkanoylamino, or two or R₄, R₅ and R₆ may form an alkylenedioxy together with two adjacent carbon atoms on the phenyl, or R₄, R₅ and R₆ may form a 5- to 7-membered ring together with the -CH₂-, and n is an integer of from 1 to 6;

(II) having the formula (II) in which:

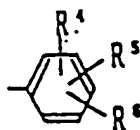
- 5 G is naphthyl or a phenyl having substituents R₁₅ and R₁₆:



10

- R₁₅ and R₁₆ being hydrogen, a lower alkyl, a lower alkoxy, a halogen, -NR₇R₈, R₇ and R₈ being hydrogen or a lower alkyl, cyano, trifluoromethyl, an alkanoylamino, trifluoroalkoxy, an alkylsulfonyl, nitro, hydroxyl, an alkylthio, and alkylsulfonylamino, an alkylcarbonylamino or a carbamoyl, or R₁₅ and R₁₆ may form a cyclic ring together with oxygen between two adjacent carbon atoms, R₁₁ and R₁₂ each are hydrogen, cyano, a lower alkyl, or a halogen or they may form a cyclic ring together with oxygen and the carbon on the phenyl, m is zero or 1, X is oxygen or sulfur, R₂ and R₃ each are hydrogen, a lower alkyl, a lower alkoxy, a cycloalkyl, a trifluoroalkyl or a lower alkenyl, or R₂ and R₃ may form a 5- to 7-membered saturated heterocyclic ring together with the nitrogen atom to which they are bonded, or R₂ may form a ring together with R₁₂, or R₃ may form a ring having a nitrogen atom together with the -(CH₂)_n-, R₂ may form a 5- to 7-membered saturated heterocyclic ring together with A, R₃ may form a 5- to 7-membered saturated heterocyclic ring together with A, A is an alkylene group having 1 to 6 carbon atoms, which alkylene may have a lower alkyl group, n is an integer of 1 to 6, J is pyridyl or a phenyl having substituents R₄, R₅ and R₆:

25



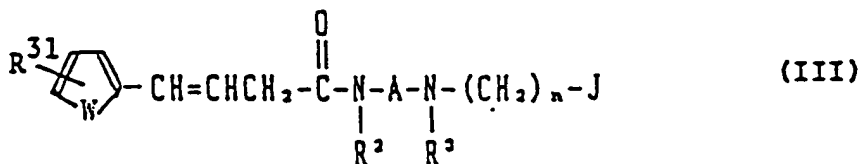
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- which R₄, R₅ and R₆ each are hydrogen, a halogen atom, a lower alkyl, a lower alkoxy, hydroxy, nitro, trifluoromethyl, an alkylsulfonyloxy, -NR₇R₈, R₇ and R₈ being hydrogen or a lower alkyl, or an alkanoylamyl, or two or R₄, R₅ and R₆ may form an alkylenedioxy together with two adjacent carbon atoms on the phenyl, or J may form a cyclic ring having a nitrogen together with the group -(CH₂)_n-; and

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(III) having the formula (III) in which in the formula (II) R₁₁ and R₁₂ are hydrogen, X is oxygen,

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- wherein R₃₁ is a hetero-aryl group, R₂ and R₃ each are hydrogen, a lower alkyl, a cycloalkyl or aryl, or R₂ and R₃ may form a 5- to 7-membered saturated heterocyclic ring together with the nitrogen and the -(CH₂)_n-, or R₃ may form a 5- to 7-membered cyclic heteroring having nitrogen or nitrogen and oxygen together with A and the nitrogen, A is an alkylene having 1 to 3 carbon atoms which may have a lower alkyl, hydroxy or a lower alkoxy group, W is oxygen, sulfur, vinylene (-C=C-) or azomethyne (-N=CH-), J is pyridyl or a phenyl having substituents, R₄, R₅ and R₆, which is hydrogen, a halogen, a lower alkyl, a lower alkoxy, hydroxy, nitro, cyano, trifluoromethyl, an alkylsulfonyloxy, -NR₇R₈, R₇ and R₈ being hydrogen or a lower alkyl group, or an alkanolamino, or two of R₄, R₅ and R₆ may form an alkylenedioxy together with two adjacent carbon atoms on the phenyl, one of R₄, R₅ and R₆ may form a 5- to 7-membered cyclic ring together with the group -(CH₂)_n-, n is an integer of 1 to 6, -(CH₂)_n- may have a lower alkyl.

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2. A 4-phenyl-3-butenolic acid derivative as claimed in Claim 1, having the formula (I) and the definition (I) and a pharmacologically acceptable salt thereof.

3. A butenolic or propionic acid derivative as claimed in Claim 1, having the formula (II) and the definition (II) and a pharmacologically acceptable salt thereof.

5 4. A 4-aryl-3-butenolic acid derivative as claimed in Claim 1, having the formula (III) and the definition (III) and a pharmacologically acceptable salt thereof.

5. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which R1 is a hetero-aryl having a nitrogen.

6. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which R1 is a 1-imidazolyl or 2-imidazolyl.

7. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which R1 is an imidazolyl.

8. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which R1 is pyridyl.

9. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which R1 is 1-imidazolyl.

10. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which R1 is pyrrolyl.

11. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which R1 is 1-pyrrolyl or 3-pyrrolyl.

12. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which n is an integer of 1 to 3.

13. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which J is the phenyl having a substituent(s), R4 is a lower alkoxy, R5 is a lower alkoxy and R6 is hydrogen.

14. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which J is m,p-dimethoxyphenyl, m-dimethoxyphenyl or m,m,p-trimethoxyphenyl.

15. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which R1 is an imidazolyl, R2 is hydrogen, R3 is methyl, J is the phenyl having a substituent(s) and R4, R5 and R6 each are hydrogen or a lower alkoxy.

16. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which R1 is 1-imidazolyl, R2 is hydrogen, R3 is methyl and J is m,p-dimethoxyphenyl.

17. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, in which is (E)-N-(3-((N'-(2-(3,5-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide.

18. The 4-phenyl-3-butenolic acid derivative as claimed in Claim 2, which is selected from the group consisting of:

30 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)butyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

35 (E)-N-[3-((N'-(2-(3,4,5-Trimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(3-pyridyl)phenyl)-3-butenamide

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(4-pyridyl)phenyl)-3-butenamide

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-pyrrol-1-yl)phenyl)-3-butenamide

40 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-butenamide

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-pyrazol-1-yl)phenyl)-3-butenamide

45 (E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1,3-oxazol-5-yl)phenyl)-3-butenamide

and

(E)-N-[3-((N'-(2-(3,4-Dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1H-pyridon-1-yl)phenyl)-3-butenamide.

19. A 4-aryl-3-butenolic or 3-aryl-2-propionic acid derivative as claimed in Claim 3, in which G is the phenyl having R15 and R16, R15 and R16 each are hydrogen, a halogen, cyano, a lower alkoxy, -NR7R8, R7 and R8 each being hydrogen or a lower alkyl, an alkylthio or an alkanoylamino, or R15 and R16 may form a cyclic ring together with oxygen and the two adjacent carbon atoms, R11 and R12 each are hydrogen, m is zero or 1, X is oxygen, R2 is hydrogen or may form a cyclic ring together with R12, A is an alkylene having 1 to 3 carbon atoms, R3 is a lower alkyl, n is an integer of 1 to 3, J is the phenyl having

20. A 4-aryl-3-butenolic or 3-aryl-2-propionic acid derivative as claimed in Claim 19, in which J is m-dimethoxy-phenyl or m,p-dimethoxy-phenyl.

21. A 4-aryl-3-butenic or 3-aryl-2-propionic acid derivative as claimed in Claim 3, which is selected from the group consisting of:

- (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-fluorophenyl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-3-(4-fluorophenyl)propeneamide,
 5 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-3-(4-cyanophenyl)propeneamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(3,4-(methylenedioxy)-phenyl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-cyanophenyl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(3,4-dimethoxyphenyl)-3-
 10 buteneamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(dimethylamino)phenyl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(methylthio)phenyl)-3-butenamide,
 15 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-chlorophenyl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-methoxyphenyl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(acetamino)phenyl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-3-(4-fluorobenzylidene)-2-pyrrolidinone
 20 and
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-3-(4-cyanobenzylidene)-2-pyrrolidinone.

22. A 4-aryl-3-butenic acid derivative as claimed in Claim 4, in which W is azomethyne.

23. A 4-aryl-3-butenic acid derivative as claimed in Claim 4, in which W is sulfur (-S-).

25 24. A 4-aryl-3-butenic acid derivative as claimed in Claim 4, in which A is a lower alkyl having 1 to 3 carbon atoms.

25. A 4-aryl-3-butenic acid derivative as claimed in Claim 4, in which R2 is hydrogen.

26. A 4-aryl-3-butenic acid derivative as claimed in Claim 4, which is selected from the group consisting of:

- 30 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(2-pyrazinyl)phenyl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(1,3-thiazol-4-yl)phenyl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(4-(2-methyl-1,3-thiazol-4-yl)phenyl)-
 35 3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(3-(1H-imidazol-1-yl)thiophene-5-yl)-3-butenamide,
 (E)-N-(3-((N'-(2-(3,4-dimethoxyphenyl)ethyl)-N'-methylamino)propyl)-4-(2-(1H-imidazol-1-yl)thiophene-5-yl)-3-butenamide,
 40 (E)-N-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-3-piperidinoethyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide,
 (E)-N-(2-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-2-pyrrolidinyloethyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide,
 (E)-N-(2-(N'-(2-(3,4-dimethoxyphenyl)ethyl)-2-pyrrolidinoethyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide,
 (E)-N-(3-(N'-(2-(3,5-dimethoxyphenyl)ethyl)-N'-methylamino)-2-hydroxypropyl)-4-(4-(1H-imidazol-1-yl)-
 45 phenyl)-3-butenamide and
 (E)-N-(1-(2-(3,4-dimethoxyphenyl)ethyl)-4-piperidinyl)-4-(4-(1H-imidazol-1-yl)phenyl)-3-butenamide.

27. A pharmacological composition which comprises a pharmacologically effective amount of the butenonic or propenonic acid derivative as defined in Claim 1 and a pharmacologically acceptable carrier.

28. The use of a propenonic acid derivative according to any of claims 1-26 for use in the manufacture of
 50 a medicament for treating, preventing, remitting or ameliorating ischemic heart disease.